Dissertation zur Erlangung des Doktorgrades
der Fakultät für Chemie und Pharmazie
der Ludwig-Maximilians-Universität München

Biomimetic Synthesis of Santalin A/B and Santarubin A/B

Synthetic Studies towards Santalin Y and Ayamenin E

von
Sebastian Strych
aus
München

2013

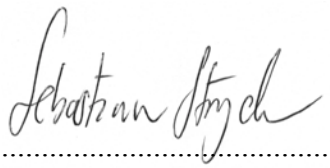
Erklärung:

Diese Dissertation wurde im Sinne von §7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Dirk Trauner betreut.

Eidesstattliche Versicherung:

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, den 14. Juni 2013



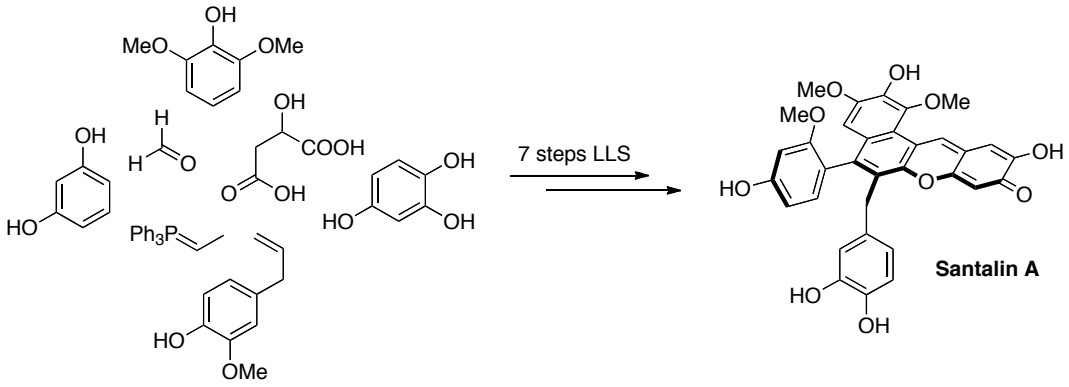
.....

Sebastian Strych

Dissertation eingereicht am:	14. Juni 2013
Erstgutachter:	Prof. Dr. Dirk Trauner
Zweitgutachter:	Prof. Dr. Paul Knochel
Mündlich Prüfung am:	15. Juli 2013

Abstract

Red sandalwood has been admired for centuries for its beautiful color, hardness and durability, especially in Asian countries. The chemical nature of its colorants, however, has long been a mystery. Almost 160 years after Pelletier's pioneering studies, the structures of the major pigments santalin A/B and santarubin A/B were elucidated by Arnone *et al* in 1975.[1] The following work is dealing with the synthesis of flavonoids and, in particular, with the members of the santalin family. The assembly of these complex natural products has been achieved in a longest linear sequence of 7 steps starting from commercially available starting material (Scheme 1).



Scheme 1 – Efficient synthesis of santalin A from commercially available starting material.

In general, the research project focuses on the development of a biomimetic synthesis of santalin A & B and santarubin A & B as well as on the complex, racemic oxafenestrane santalin Y.[2] Especially fascinating is the biosynthetic connection of these fundamentally different structures, which are believed to arise from two simple, achiral building blocks. In this work the limits of biomimetic synthesis were tested and it was tried to find out whether this natural products could be assembled along biosynthetic lines, without the necessity of enzymatic catalysis.[3] A formal 4+2 cycloaddition and oxidiation cascade was assumed to give rise of benzoxanthenone natural products (santalin A/B and santarubin A/B), while a formal 3+2 cycloaddition followed by Friedel-Crafts cyclization was envisioned for the formation of santalin Y.

For a unified synthesis of these family members, a robust and scalable route to the common precursor, namely anhydrobase was necessary. This was achieved by novel methods using a zinc-base mediated Negishi cross–coupling developed by the group of Prof. Knochel.[4] Preparation of benzylstyrenes, could be achieved by using novel allylation strategies, including a π-allyl Suzuki coupling,[5] Friedel-Crafts allylation[6] and olefin cross-metathesis.[7] The tested biomimetic conditions were successful in the synthesis of santalin AC, santalin A and B and santarubin A and B. However the conditions applied have not resulted in santalin Y. In the course of overcoming selectivity problems, deeper insight in the reactivity of anhydrobase and benzylstyrenes has been gained and could serve to unravel new reactivities and methods in flavonoid chemistry.

Acknowledgements

First of all, I want to thank Prof. Dr. Dirk Trauner for his supervision of my work over the last 4 years. I cannot thank enough for giving me an intellectual challenging project, the freedom to test myself in the field of total synthesis, the trust in my work as well as the freedom to explore new ideas and solve problems at hand.

I am very thankful to Prof. Dr. Paul Knochel for agreeing to be the second reviewer of this thesis as well as Prof. Dr. K. Karaghiosoff, Prof. Dr. F. Bracher, Prof. Dr. A. Hoffmann-Röder and Prof. Dr. em. W. Steglich for accepting to be co-reviewers.

Especially, I am very grateful to Desiree Stichnoth, Julien Lefranc, Filip Bihelovic and Giulio Volpin for careful proofreading of this work.

I want to thank all past and present members of the green lab Philipp Stawski, Daniel Hog, Matthias Schönberger, Timm Fehrentz (chronologically) for the excellent lab atmosphere and intellectual support.

I am very thankful to my students Jakob Franke, Hinnerk Saathoff, Robin Meier, Jessica Steinbacher, Jonathan Wieser, Martin Maier and Antonio Fernandez Vargas for their hard work and input.

Furthermore, I want to thank for support provided by the Trauner group staff Petra Böhrer, Heike Traub, Dr. Martin Sumser, Tobias Kauer, Carrie Louis, Luis de la Osa de la Rosa for their help in organizing my chemical life, and as well as the analytical team of the LMU for their invaluable help.

I want to thank all past and present Trauner group members, which I had the pleasure to meet during my time at the LMU.

Finally, I am deeply thankful to Desiree Stichnoth and my family for their never-ending support.

Table of Abbreviations

Å	Ångström (10^{-10} m)
Ac	acetyl
aq.	aqueous
ATR	attenuated total reflection
br	broad
Bn	benzyl
Bu	butyl
c	concentration
CAN	ceric ammonium nitrate
CCDC	Cambridge crystallographic data center
CoA	Coenzyme A
COSY	^{1}H correlation spectrospcopy (NMR)
cy	cyclohexyl
d	days
d	deutero
δ	chemical shift (ppm)
Δ	delta, difference
dba	dibenzylideneacetone
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMP	Dess-Martin periodinane
Dppf	1,1'-*bis*(2-diphenylphosphinophenyl)ferrocene
E	opposite, *trans*
EI	electron ionization
eq.	equivalent(s)
ESI	electronspray ionisation
Et	ethyl
g	gram(s)

h	hour(s)
Hex	hexanes
HMBC	heteronuclear multiple bond connectivity (NMR)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence (NMR)
Hz	hertz
i	*iso*
IBX	2-iodoxybenzoic acid
IR	infrared
J	coupling constant
L	liter(s)
λ	lambda, wave length unit
LLS	longest linear sequence
m	meter(s)
m	*meta*
M	molar
Me	methyl
Mes	mesitylene
min	minute(s)
mol	mole(s)
m.p.	melting point
Ms	mesylate
MS	mass spectrometry
m/z	proportion mass/charge
N	normal
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NMO	*N*-methylmorpholine-*N*-oxide
NOESY	nuclear overhauser enhancement and exchange spectroscopy
Nu	nucleophile
o	*ortho*

p	*para*
PCC	pyridinium chlorochromate
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
Ph	phenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
*p*TSA	*para*-toluenesulfonic acid
py	pyridine
Pr	propyl
quant.	quantitative
R_f	retardation factor
RP	reversed phase
r.t.	room temperature
s	second(s)
sat.	saturated
RuPhos	2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	temperature
t	*tert*
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TPAP	tetra-*n*-propylammonium perruthenate
UV	Ultra-violet
W	Watt
X-ray	X-radiation
Z	together, *cis*

Table of Contents

I. Flavonoids and the Major Constituents of Red Sandalwood

Flavonoidic structures stem biosynthetically from the shikimic acid and the polyketide pathway.[8] Structures derived from this combined biosynthetic origin are widely distributed in plants and present polyphenolic systems. While in general phenolic structures are believed to be rather simple, this class shows a huge diversity by means of complexity, varying states of oxidation and biological function (Figure 1).[9]

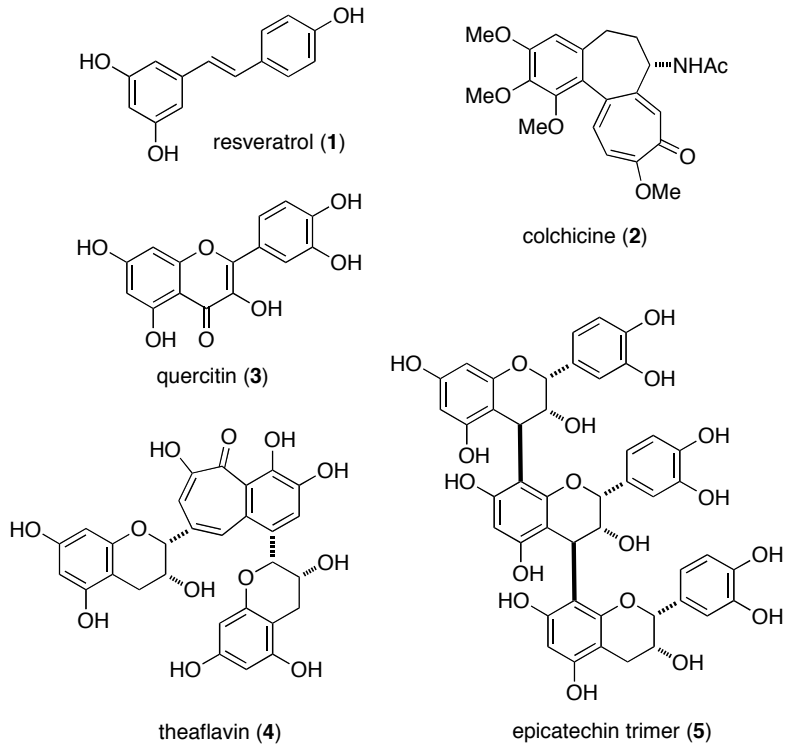
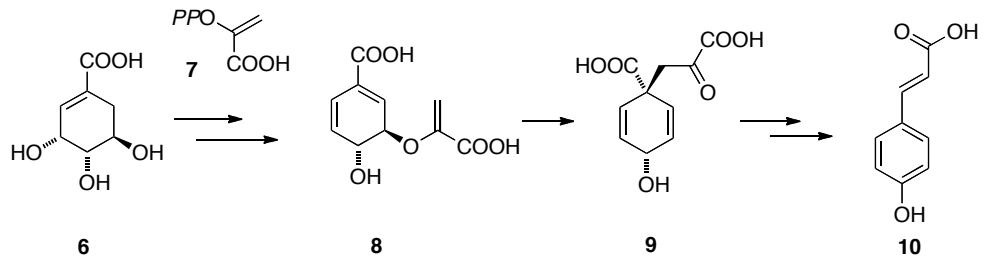


Figure 1 – Structural diversity of polyphenolic structures.

The polyphenolic structures shown in Figure 1 give an impression of the diversity in this class, starting from rather simple stilbene structures such as resveratrol (**1**)[10] to flavones, for example quercitin (**3**), to dimers (**4**) and trimers (**5**) of flavone units. Biosynthetically, the oligomeric structures can be made by oxidative couplings. This is possible because of the presence of easily oxidizable catechol and pyrogallol

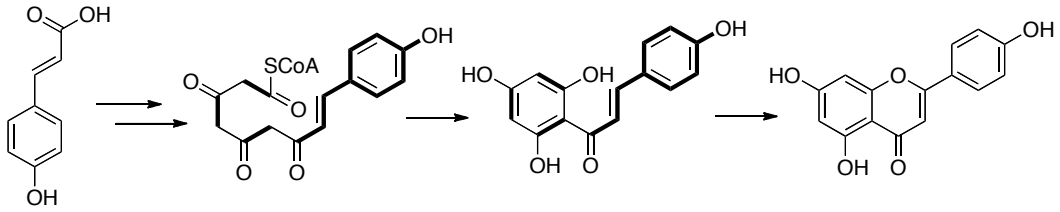
units.[9c] More diverse functionalization is observed in presence of an amino function, for example in colchicine (**2**).[11]

As mentioned before, the flavonoidic structures can be drawn back biosynthetically to shikimic acid (**6**) (Scheme 2), which, upon linking of a unit of enol pyruvate (**7**), finally leads to chorismic acid (**8**). An enzyme-catalyzed Claisen rearrangement results in prephenic acid (**9**), the precursor of aryl pyruvic acids. Further functionalization by pyridoxal phosphate dependent transaminases (PPT) finally yields the amino acids phenylalanine and tyrosine. The transformation from amino acids to coumaric acid (**10**) has been shown to be an elimination of ammonia to generate the phenylpropanoid. Coumaric acid is the precursor for a wide range of natural products produced in plants.[8]



Scheme 2 – Plant phenols stem from shikimic acid.

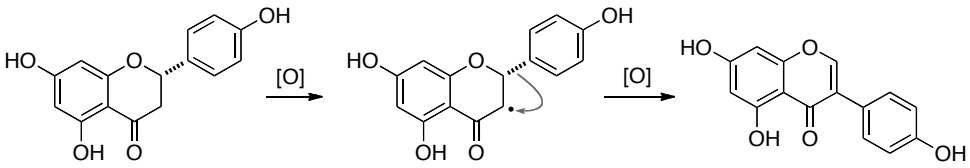
Coumaric acid itself reacts further in two distinct pathways. One is the oxidative modification of its core resulting in phenylpropanoid structures, for example, lignans, lignines or coumarins. Another possibility for functionalisation is the integration of coumaric acid into the polyketide synthase pathways. This elongation of a phenylpropanoid starter unit by C2 units, derived from malonyl-CoA can react further by reduction and dehydratisation processes into the class of stilbenes and flavonoids (Scheme 3). Enzyme catalyzed folding domains facilitate the formation of polyketide structures (**11**) to chalcone **12** similar to a Claisen reaction. In presence of *ortho*-hydroxy groups, an intramolecular Michael attack and reoxidation can lead to the flavonoids, which are found in a huge diversity throughout the plant kingdom.



10 11 12 13

Scheme 3 – Chalcones and flavones can be made along the shikimic acid and the polyketide pathway.

While these structures follow a linear pathway towards complexity, isoflavones show a skipped phenyl ring on the adjacent carbon atom. The mechanism of this rearrangement has not been completely elucidated, but it is believed that starting for example from naringenin **14** a NADPH and oxygen codependent radical mechanism *via* **15** is responsible for the migration of the phenyl ring to yield isoflavone **16** after oxidation (Scheme 4).



14 15 16

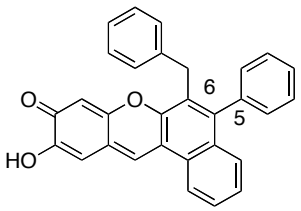
Scheme 4 – Interconversion of flavones to isoflavones using a radical mechanism.

As isoflavonoidic structures are widely spread in plants, the function of these natural products is not fully understood. Due to the presence of easily oxidizable aromatic hydroxy groups, the main purpose is believed to be protection from highly reactive radicals formed by oxygen.[9c] This is seen in the fact that most of the so far isolated polyphenolic structures show antioxidative activity, which protect living organisms from oxidative stress. Oxidative stress is believed to cause a variety of age dependent diseases like Alzheimer, Parkinson, amytrophic lateral sclerosis (ALS) and more.[12] Therefore, a deep understanding of antioxidative substances is essential in understanding, preventing, and treating these diseases.

Due to the presence of large conjugated π-systems, polyphenolic structures tend to show strong and bright colors. Some of these colorants have been used for centuries as dyes in the field of textiles and furniture. An example for these very colorful plants is the hardwood of red sandalwood. This unique colored wood has fascinated and influenced many people in different cultural historical contexts. In Asian countries, where this remarkable tree is cultivated, red sandalwood was used in religious contexts or as highly valued furniture in imperial households. These applications show the desire of humans for beautiful and appealing colors. Objects carved from the red hardwood (Figure 2) were reserved only for a few people.

Figure 2 – Objects carved from the red hardwood of sandalwood.

In 1814 Pelletier's pioneering studies tried to shine light into the structural details of these coloring matters.[13] Due to the complex mixtures of different grades of oxidation and different methylation patterns, the structures of the main colorants could not be elucidated for more than one century. In the 1970's, studies towards the elucidation of these natural products became again more prominent as a structure was proposed for santalin A and B.[14] This proposal could be corrected later by a series of studies carried out by the group of Arnone in 1975.[1, 15]



6-benzyl-10-hydroxy-5-phenyl-9*H*-benzo[*a*]xanthen-9-one

Figure 3 – The core of the santalins and santarubins.

While the elucidated structures of santalin A,B (17, 18) and santarubin A,B (19, 20) share the same core, the substitution pattern, including the oxidation state and methylation, varies. The core of the red colorants shows a unique 9*H*-benzo[*a*]xanthenone structure (Figure 3), which centers a highly substituted naphthalene core. They differ in the substitution of their phenyl substituent at C5, which can either bear a resorcinol pattern (santalins) or a catechol pattern (santarubins). The opposite is true for the benzyl substituent in position 6 as shown in **Figure 4**.

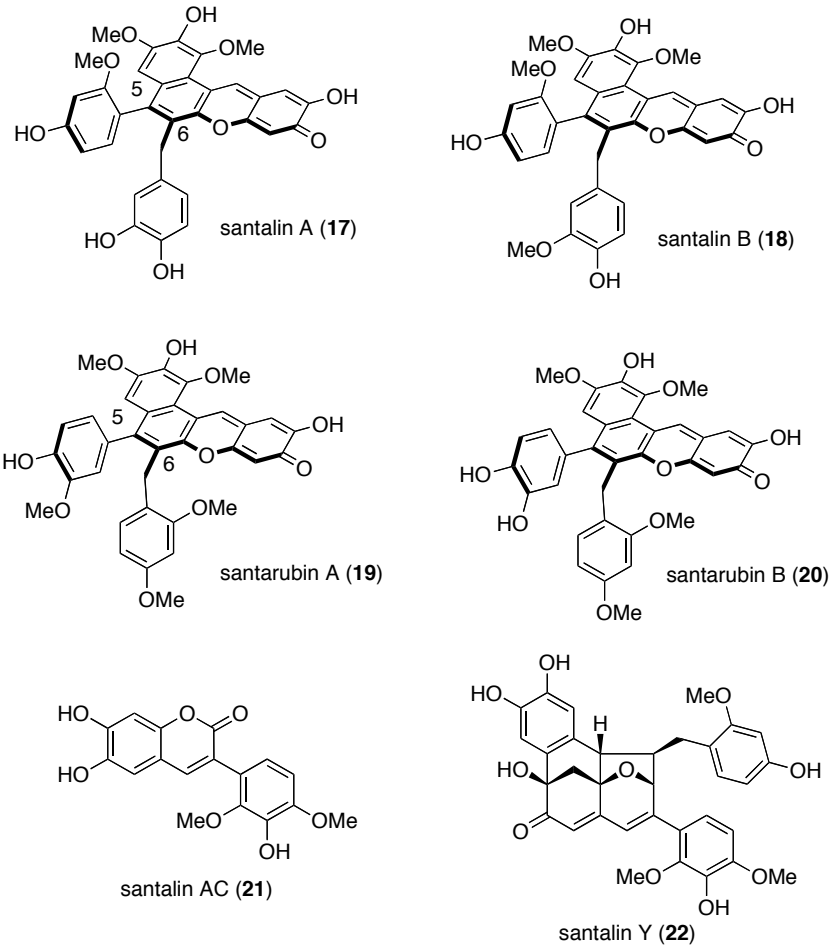


Figure 4 – The major colorants of red sandalwood.

In 1995 the group of Kinjo reexamined the red hardwood of *Pterocarpus santalinus* and isolated two minor colorants besides the already known santalins A & B and santarubins A & B.[2] Santalin AC (**21**), a coumarin, and santalin Y (**22**), a rather complex natural product could be obtained. Santalin Y occurs as a racemate and has five stereogenic centers, a highly functionalized oxafenestrane as well as phenyl and benzyl substitutents directly attached to this core. The proposed structure could be verified by a crystal structure shown in Figure 5. It impressively depicts the bend, convex structure of santalin Y.

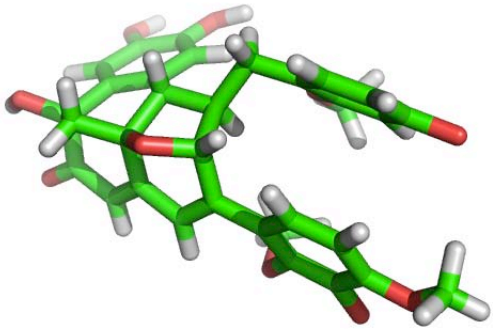
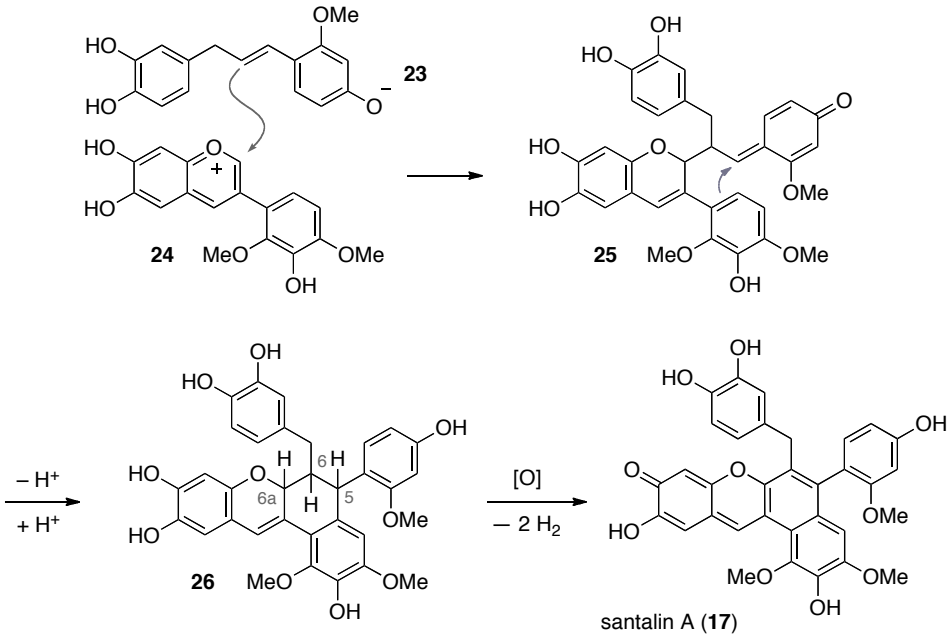


Figure 5 – Crystal structure of santalin Y.

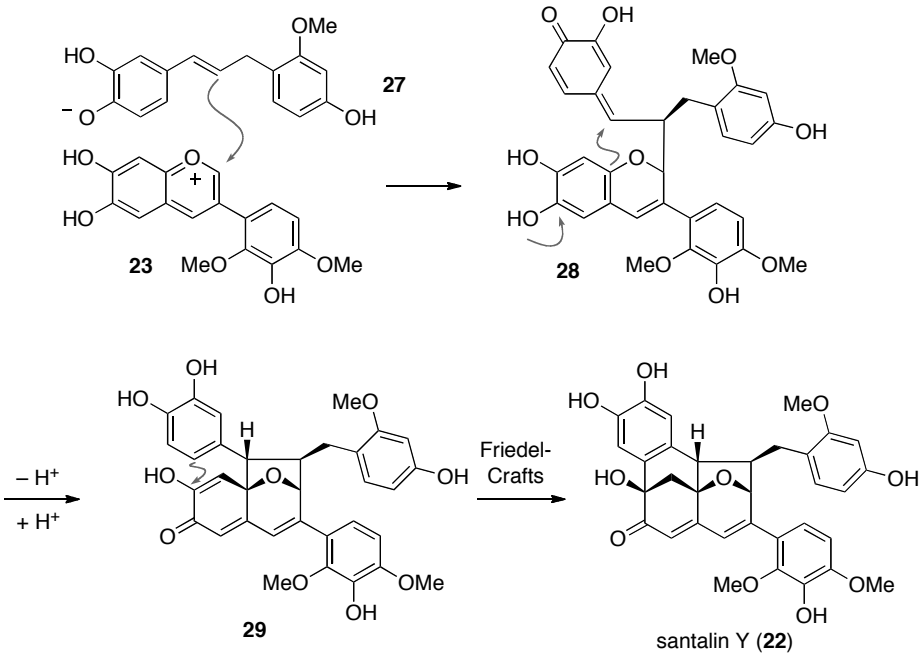
The isolation of santalin AC and santalin Y from red sandalwood lead to a biosynthetic proposal for the class of santalins and santarubins, focusing on one precursor for the formation of all members.[2]

The proposed structure can be traced back to isoflavylium cation **24**, which can react further through a vinylogous attack of a benzylstyrene **23** to the most electrophilic site of the benzopyrylium cation. The resulting reactive quinone methide **25** can be attacked by the neighboring electron rich pyrogallol unit. The formed tetracyclic core structure **26** shows very labile C-H bonds in positions 5, 6 and 6a and a labile phenolic H bond, which are supposed to be oxidized instantly after the cycloaddition (Scheme 5).



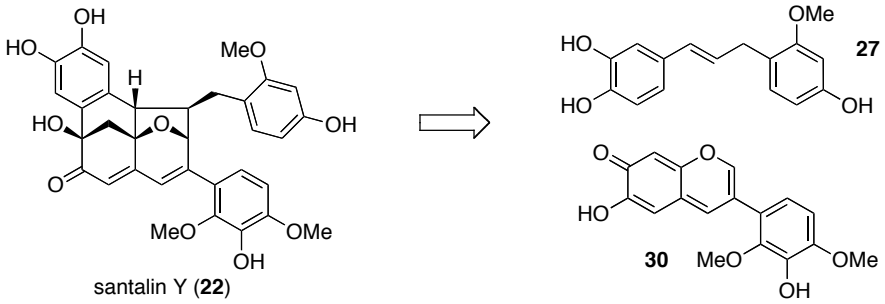
Scheme 5 – Biosynthetic proposal for the formation of santalin A.

The same is true for the formation of santalin Y. A benzylstyrene isomeric to **23**, with respect to the double bond position, attacks in the same manner as for santalin A, but the formed quinone methide **28** is nucleophilically attacked by the catechol unit of the formed benzopyran unit resulting in dearomatized structure **29**. It is believed that this strained system reacts further through a Friedel-Crafts cyclization after tautomerisation of the hydroxyketone, leading to santalin Y (**22**) in a concerted fashion (Scheme 6).



Scheme 6 – Biosynthetic proposal for the formation of santalin Y.

II. Synthetic Studies towards Santalin Y & Ayamenin E and Synthesis of Santalin AC



Scheme 7 – Retrosynthetic analysis for santalin Y.

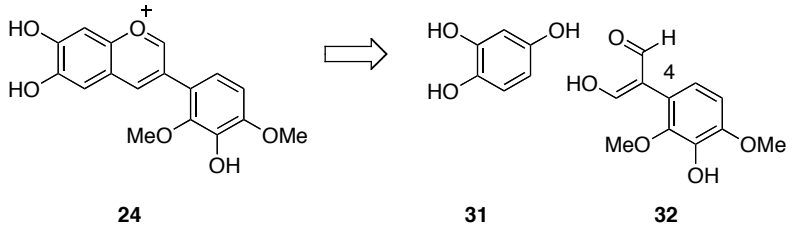
The elaboration of a biosynthetic proposal, based on the presence of benzoxanthenone dyes and racemic santalin Y, prompted us to investigate a synthesis of this class along this biosynthetic assembly line (retrosynthesis is shown in Scheme 7).[2]

Therefore, a robust synthetic route for isoflavylium cation **24**, as well as for the benzylstyrene building block **27** was needed. In this chapter, the different strategies towards the formation of isoflavylium unit **24** are described. A subchapter describes the preparation of benzylstyrene **27** by means of olefin cross-metathesis from two rather simple building blocks. With this proposed precursor in hand the biosynthetic proposal has been tested and will be presented in the final subchapter.

II. 1. Preparation of Anhydrobase 30

II. 1. 1. Friedel-Crafts cyclization approach

Studies towards the family members of red sandalwood started with investigations for a robust preparation of isoflavylium **24** or anhydrobase **30**, respectively. Literature precedence has raised hope to enter this class of compounds by a four step sequence starting from pyrogallol, attaching a functional handle at the C4 position (Scheme 8). These functionalized phenols are known to react further with symmetric phenols in an intermolecular Friedel-Crafts arylation under strong acidic conditions providing a benzopyrylium **24** in one step (Scheme 8).[16]

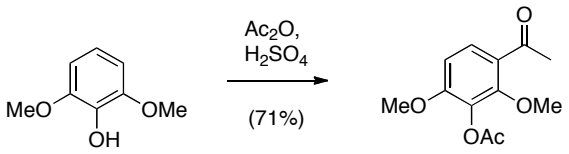


24 **31** **32**

Scheme 8 – Retrosynthesis for the formation of isoflavylium salt from malonyldialdehyde **32**.

II. 1. 1. 1. Approach to aryl malonyldialdehyde 32 *via* Willgerodt-Kindler & studies towards Ayamenin E

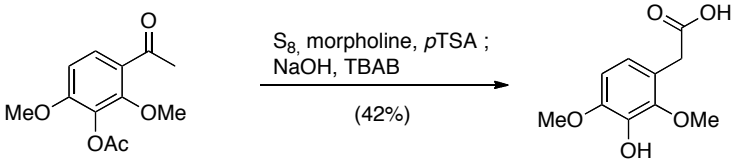
The first entry started with functionalization of pyrogallol **33** by a Friedel-Crafts acylation using acetic anhydride.[17] This reaction yielded acetopyrogallol **34** in acceptable yields with concomitant protection of the phenol. The only observed side-product was acetylated pyrogallol, which suggests, that the phenolic group is protected first, directing the Friedel-Crafts acylation strongly in the favored C4 position (shown in Scheme 9).



33 **34**

Scheme 9 – Friedel-Crafts acylation gives entry to acetophenol.

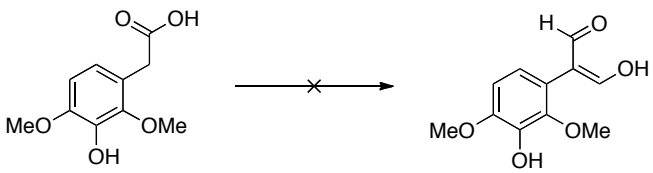
The following step was an oxidative transposition of the carbonyl group to form aryl acetic acid **35** in one step under Willgerodt-Kindler conditions (Scheme 10).[18] The mechanism of this reaction is still in debate, but it is believed that the formed thiocarbonyl amide is hydrolyzed under basic conditions, which in this case deprotects the acetylated phenol in the same step. Aryl acetic acid **35** was obtained in moderate yield.



34 **35**

Scheme 10 – Willgerodt-Kindler Reaction transposes the carbonyl function.

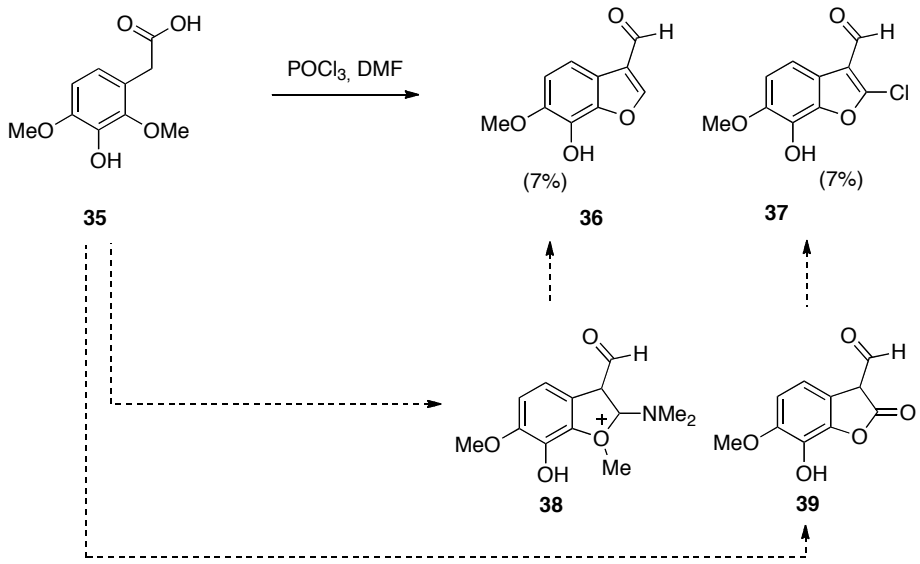
Next, treatment of phenyl acetic acids with an excess of *in situ* generated Vilsmeier's chloroiminium reagent formylates the benzylic position twice, which upon heating would decarboxylate. The presence of either a hydroxy or methoxy group in *ortho*-position to the benzylic position seems to hamper the reaction, which has been proven to work smoothly with the simpler phenyl model system (Scheme 11).[19]



35 **32**

Scheme 11 – Decarboxylative formylation under Vilsmeier-Haack conditions failed.

The presence of an *ortho*-hydroxy group facilitated the formation of substituted benzofuran systems, either simple **36** or chlorinated **37** as a mixture. It is believed that during the formylation under acidic conditions ($POCl_3$) an interruption takes place, which forms an instable oxonium ion **38** at the methoxy group, which is deprotected to form the furan ring. Chlorination may result from chloride substitution from a generated benzolactone **39** (Scheme 12).



35 **36** **37** **38** **39**

Scheme 12 – Vilsmeier-Haack conditions give rise of benzofuran aldehydes **36** and **37** and their proposed intermediates **38** and **39**.

While milder variants of this method were tested, it became clear that under no conditions the aryl malonyldialdehyde could be formed, always favoring the formation of the previously mentioned benzofurans in different ratio.

Providing the highly functionalized chlorobenzofuran aldehyde **37** in a short step sequence, it was realized that this can give a fast entry to the isoflavone derived natural product ayamenin E (**40**)[20]. Benzofuran **37** displays two electrophilic positions, which could be potentially attacked by phloroglucinol **41** to assemble the reduced form of ayamenin E with respect to the benzylic alcohol. In Figure 6 the two building blocks are shown, which could be fused by a formal 3 + 3 cycloaddition. This could happen *via* attack of the chlorinated Michael-system by the phenolic

function of phloroglucinol. A Friedel-Crafts cyclization could close the ring to form the tetracyclic system.

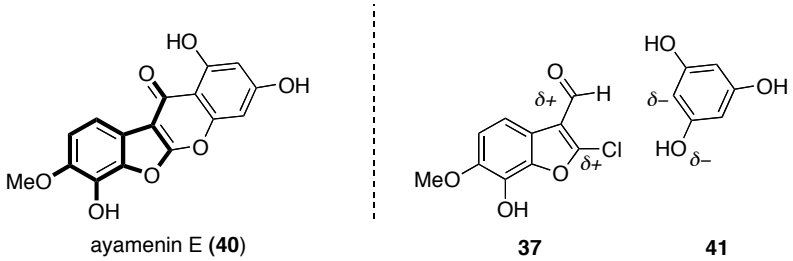
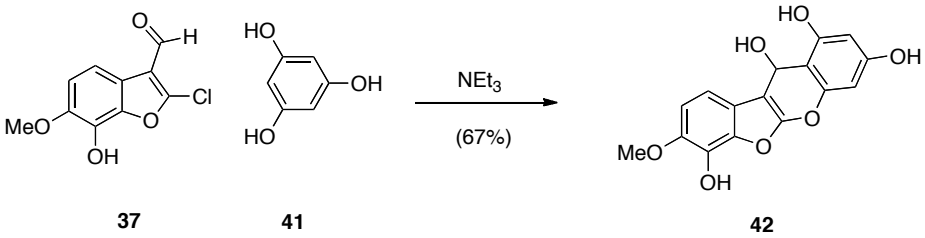


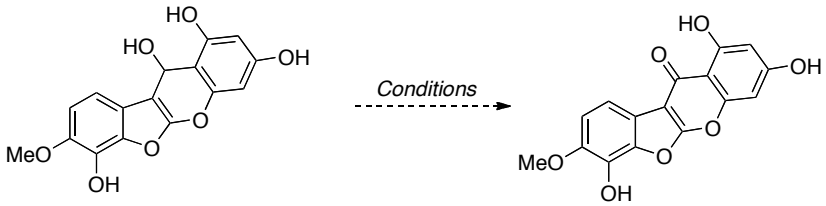
Figure 6 – Ayamenin E (benzofuran precursor in bold).

A reaction took place in presence of a weak base (NEt_3) at elevated temperatures. Formation of benzylic alcohol **42** was proposed and tested in the subsequent oxidation step (Scheme 13).



Scheme 13 – 3 + 3 cycloaddition gives rise of the proposed structure **42**.

Final oxidation of the benzylic alcohol has been shown to be more complex than anticipated and failed under various oxidation conditions (Table 1).



42 **40**

Entry	Reagent	Solvent	Equivalents	Conclusion
1	MnO_2	CH_2Cl_2	50	c.m.
2	TPAP/NMO	MeCN	1.5	c.m.
3	IBX	EtOAc	2	c.m.
4	DMP	EtOAc	3	c.m.
5	PCC	CH_2Cl_2	1	c.m.

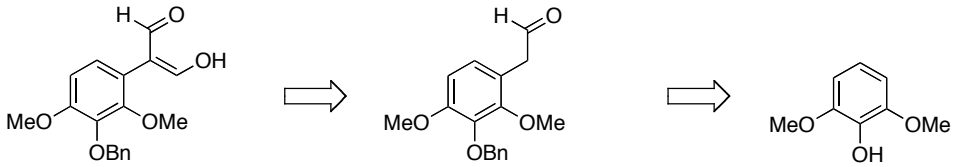
c.m. = complex mixture.

Table 1 – Conditions tested for the oxidation of benzylic alcohols.

One of the reasons for the formation of complex mixtures could be addressed to the strong intercalation of the phenolic proton and presence of free phenolic groups, making this group less prone to oxidation.

II. 1. 1. 2. Approach to aryl malonyldialdehyde 43 *via* DMF acetal

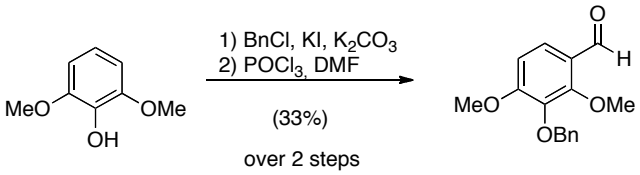
As shown previously, formation of malonyldialdehyde under acidic conditions resulted in side reactions, which could not be overcome. This lead to the insight that formylation of aryl acetaldehyde under milder, neutral conditions could give compound **43**. This strategy starts from pyrogallol unit **33**, as the reduction of aryl acetic acid **35** to aldehyde **44** failed, resulting only in a complex mixture (Scheme 14).



43 **44** **33**

Scheme 14 – Retrosynthesis of alternative ways to yield aryl malonyldialdehyde.

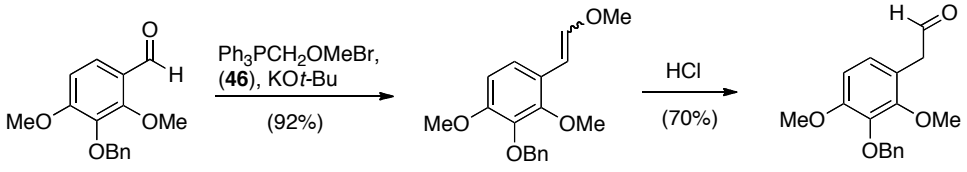
Pyrogallol **33** afforded benzyl ether and subsequent Vilsmeier-Haack formylation resulted in benzaldehyde **45** in moderate yield over two steps (Scheme 15). [21]



33 **45**

Scheme 15 – Benzaldehyde was formed via Vilsmeier-Haack formylation.

Homologation of benzaldehyde **45** was achieved under Wittig conditions using **46** in very good yields.[22] Subsequent deprotection had to be carried out at low temperatures to avoid aldol side reactions. Aryl acetaldehyde **44** was obtained in good yields (Scheme 16).

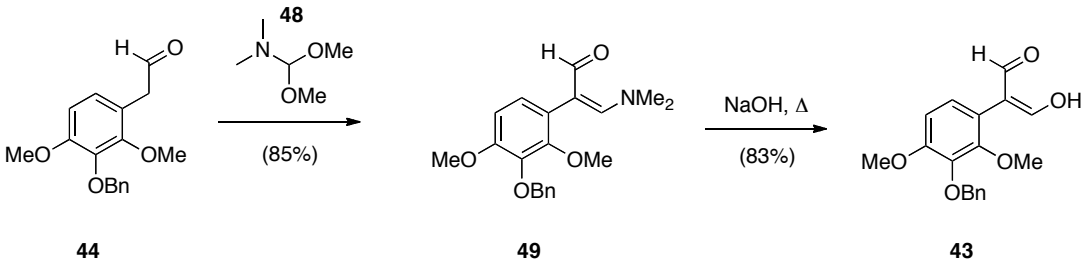


45 **47** **44**

Scheme 16 – Homologation using Wittig-Kluge reaction.

Dimethylamino acrolein **49** could be formed using dimethyformamide dimethyl acetal (**48**) in DMF at room temperature. This reagent is known to formylate α-carbonyl groups under mild conditions.[23] Hydrolysis of the dimethylamino function using

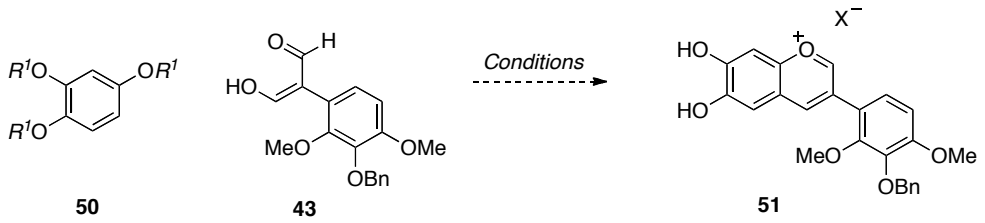
strong basic conditions afforded aryl malonyldialdehyde **43** in good yields. It is noteworthy, that these products can act as bidentate ligands with coordinating metals forming complexes (Mg^{2+}, Ca^{2+}), thus decreasing the yield of this reaction (Scheme 17).



44 **49** **43**

Scheme 17 – Formation of aryl malonyldialdehyde under mild conditions.

With malonyldialdehyde **43** in hand, the stage was set to investigate the Friedel-Crafts type formation of isoflavylium salt.[16a] While literature describes formation of benzopyrylium salts with symmetric phenols (e.g. phloroglucinol), these results show that unsymmetrical catechol phenol coupling partners **50** are not suitable for the reaction. The catechol moiety seems to be a weak directing group for this aromatic substitution reaction. A wide survey of different substitution at the phenol groups as well as various strong and non-nucleophilic acids showed either decomposition or formation of complex mixtures (Table 2).



Entry	Acid	Solvent	R^1	Conclusion
1	$HClO_4$	AcOH	H	decomp.
2	HCl	Et_2O	H	c.m.
3	HBF_4	AcOH	H	decomp.
4	HPF_6	AcOH	H	decomp.
5	$HClO_4$	AcOH	Ac	decomp.
6	HBF_4	AcOH	Ac	decomp.
7	HPF_6	AcOH	Ac	decomp.

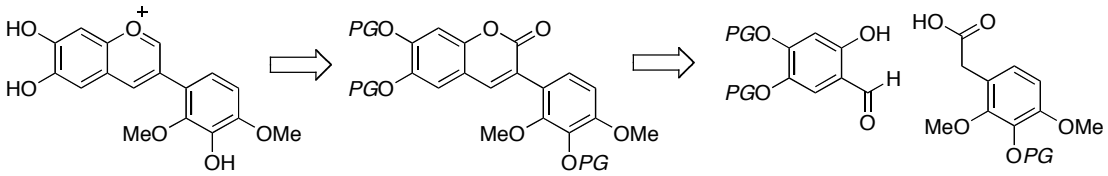
decomp. = decomposition; c.m. = complex mixture.

Table 2 – Attempts for the formation of isoflavylium salt **51**.

After this result, the strategy had to be changed to form the benzopyrylium salt from a preformed isoflavonoidic structure.

II. 1. 2. Knoevenagel approach

An alternative route to benzopyrylium salts can be achieved by reducing either coumarins or flavones to the corresponding lactol or benzylic alcohol by subsequent treatment with acidic agents. Synthesis of coumarin **52** by Knoevenagel conditions lead to two building blocks, benzaldehyde **53** and phenyl acetic acid **54**, which can be seen in Scheme 18. Preliminary attempts using available pyrogallol acetic acid **35** and commercially available free hydroxy benzaldehyde lead with the reported conditions to the desired coumarin in poor yields.[24]

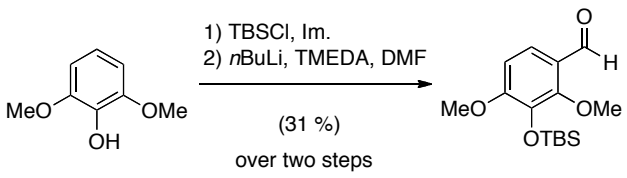


24 **52** **53** **54**

Scheme 18 – Retrosynthesis for the formation of isoflavylium cation from coumarin **52** by Knoevenagel approach.

The synthesis commenced with the preparation of phenyl acetic acid starting from pyrogallol unit **53**. Therefore two competing routes for the preparation the silylated benzaldehyde **55** were carried out. One approach focused on *ortho* directed metalation using methoxy as coordinating groups and as an alternative lithium-halogen exchange to yield benzaldehyde **55** was attempted.[25]

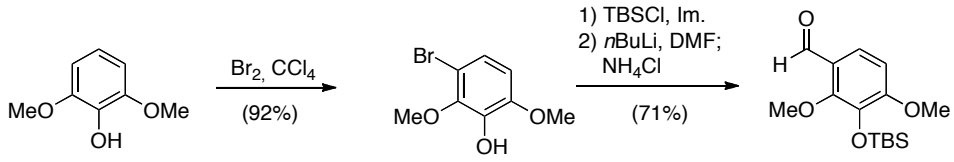
Due to the shorter sequence *ortho*-directed metalation was investigated. The first synthesis started with TBS protection of pyrogallol unit **33** affording silyl ether **56** in very good yield. Trapping the metalated species with DMF resulted in benzaldehyde **55** in poor yield. For optimization TMEDA, a salt breaking additive, was added to improve the yield (Scheme 19).



33 **55**

Scheme 19 – Formylation using *ortho*-directed metalation.

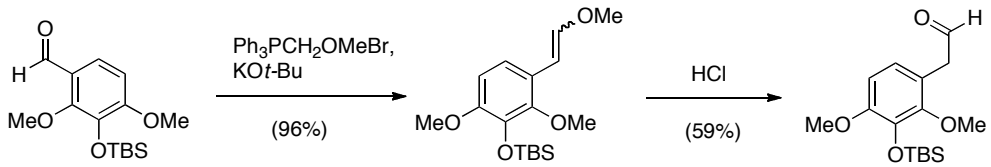
Alternatively, metalation from brominated phenol **57** was attempted.[26] Literature known compound **57** was protected with a TBS group and showed very good halogen-lithium exchange ability, resulting in benzaldehyde **55** after trapping the lithiated species with DMF and hydrolysing under acidic conditions (Scheme 20).



33 **57** **55**

Scheme 20 – Formylation using lithium-halogen exchange.

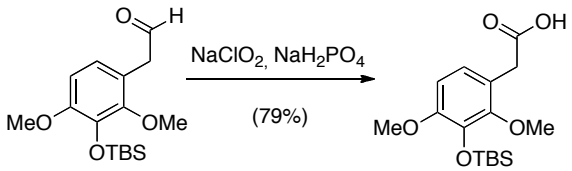
In analogy to the previously described route, benzaldehyde **55** was homologated using Wittig-Kluge conditions and enol ether **57** was deprotected under acidic conditions at low temperatures resulting in aldehyde **58** (Scheme 21).[22]



55 **57** **58**

Scheme 21 – Homologation using Wittig-Kluge conditions.

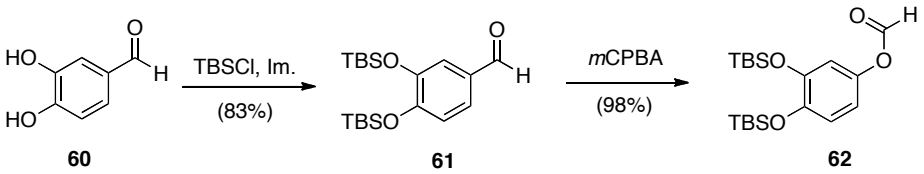
Pinnick oxidation of aldehyde **58** resulted in silylated aryl acetic acid **59** in good yield over 6 steps (Scheme 22).



58 **59**

Scheme 22 – Oxidation using Pinnick conditions.

The synthesis of *ortho*-hydroxy benzaldehyde **63** started with the protection of commercially available benzaldehyde **60** with TBS groups resulting in silyl ether **61**. Bayer-Villiger oxidation of benzaldehyde **61** resulted in formyl ester **62** in quantitative yield, giving the substrate for a Fries-rearrangement and an *ortho*-directed formylation (Scheme 23).



60 61 62

Scheme 23 – Preparation of formylphenol **62** using mCPBA.

Fries rearrangement worked after careful optimization with boron trichloride as catalyst in low yields.[27] Due to low yields of this reaction, we changed the strategy to introduce the formyl group stepwise (Table 3).

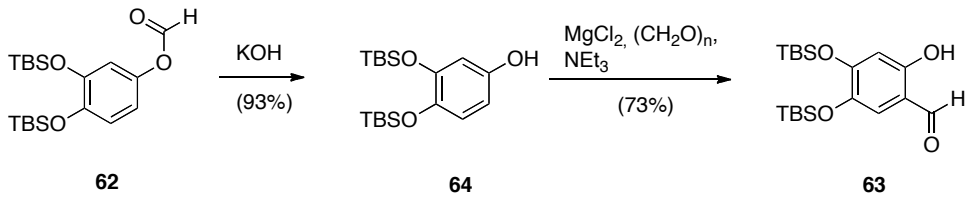
62 63

Entry	Catalyst	Solvent	Yield
1	$EtAlCl_2$	CH_2Cl_2	5%
2	$AlCl_3$	CH_2Cl_2	decomp.
3	Et_2AlCl	CH_2Cl_2	traces
4	BCl_3	$C_2H_4Cl_2$	26%

decomp. = decomposition.

Table 3 – Optimization of Fries rearrangement using different catalysts.

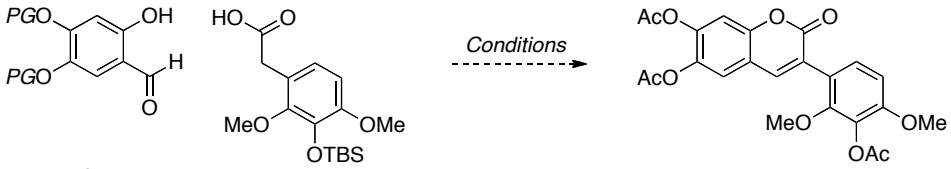
We therefore changed to the *ortho*-directed formylation by deprotection of phenyl formyl ester **62**, resulting in a phenolic hydroxy group in **64**. Following literature, introduction of a formyl group can be directed by an adjacent hydroxy group.[28] This method facilitates a Lewis-acid directed redox mechanism using phenolic hydroxy groups to direct and resulted in benzaldehyde **63** in good yield (Scheme 24).



62 64 63

Scheme 24 – Stepwise approach to *ortho* hydroxy benzaldehyde **63**.

With the two building blocks in hand, the Knoevenagel coumarin synthesis was attempted. The harsh conditions of this method afforded always the peracetylated coumarin product **65**. Best results were obtained by slow addition of arylacetic acid **59** to benzaldehyde **53** in presence of potassium acetate in acetic anhydride (Table 4).



53 59 65

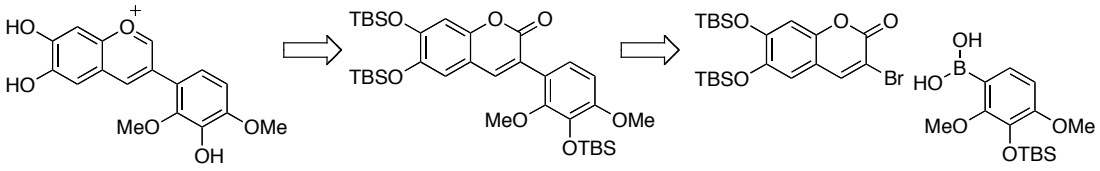
Entry	Base	Solvent	Ratio 53:59	PG	Yield
1	KOAc	Ac_2O	2:1	H	traces
2	KOAc	Ac_2O	1:2	H	7 %
3	NaOAc	Ac_2O/toluene	1:1	TBS	14 %
4	KOAc	Ac_2O/toluene	1:1	TBS	15 %
5	NaOAc	Ac_2O	1:1	TBS	22 %
6	KOAc	Ac2O	1:1	TBS	24 %

Table 4 – Optimization of Knoevenagel coumarin synthesis.

Unfortunately the unsatisfactory low yield made further investigation of this route impossible, due to the wasteful amounts of material needed for the preceding steps.

II. 1. 3. Suzuki coupling approach

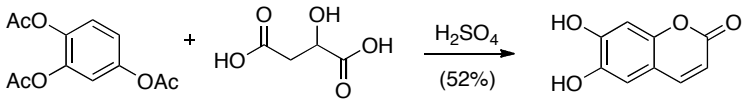
Instead of forming the oxygen containing coumarin ring system in one step, the coumarin fragment is assembled first and the pyrogallol unit is attached in a second step. It is known from literature that cross-coupling reactions using aryl boronic acids lead to coumarin structures (Scheme 25).[29]



24 **66** **67** **68**

Scheme 25 – Retrosynthesis for the formation of the isoflavylium cation from coumarin *via* Suzuki approach.

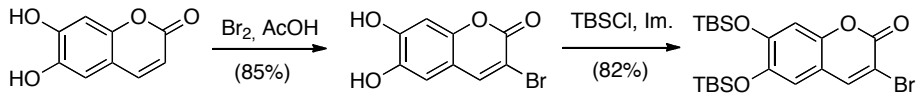
Following this strategy, the first step was the literature known preparation of esculetin **71** using commercially available substances which gave the desired product in moderate yields (Scheme 26).[30] Due to the cheap availability of the starting materials, large amounts of esculetin could be prepared in one operation (15 g scale).



69 **70** **71**

Scheme 26 – Formation of esculetin using a decarboxylative oxidation mechanism.

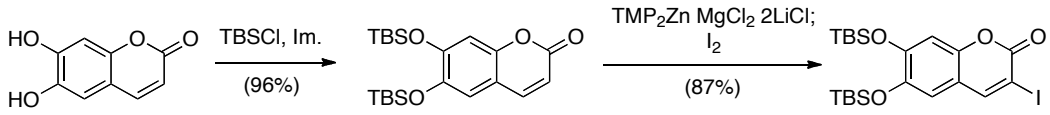
Bromination of esculetin **71** gives rise to bromocoumarin **72** in good yield and as a single regioisomer. Silyl protection of **72** was achieved under standard conditions giving the halogen-coupling partner **67** in good yield (Scheme 27).



71 72 67

Scheme 27 – Formation of bromoesculetin.

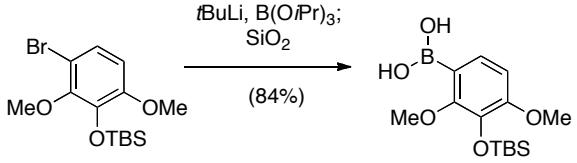
As an alternative to the bromo coupling partner, a method developed by the group of Prof. Knochel was used to yield iodocoumarin **74** from TBS protected esculetin **73** in very good yields.[4a] This method allows a diaminozinc base to regioselectively deprotonate coumarins in the α-position (Scheme 28).



71 73 74

Scheme 28 – Formation of iodo esculetin facilitating directed metalation.

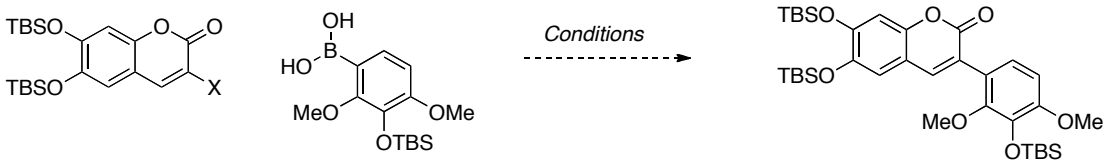
The readily prepared aryl bromide **75** can be transformed to the boronic acid **76** in a single operation through halogen-lithium exchange, trapping of the anionic species with borate and hydrolysis of boronic ester to the corresponding acid using silica (Scheme 29).[31]



75 76

Scheme 29 – Formation of boronic acid by lithium halogen exchange.

With the two coupling partners in hand, the cross-coupling was tested under various conditions (Table 5).



67/74 **76** **66**

Entry	Catalyst	Ligand	X	Solvent	Ratio 67/74:76	Conditions	Yield
1	$Pd(PPh_3)_4$	-	Br	benzene	1:1	21 h/ 70°C	traces
2	$Pd(PPh_3)_4$	-	Br	DMF/H_2O	1:1	1 h/ 70°C	deprot.
3	Pd_2dba_3	SPhos	Br	toluene	1:1	50 h/ 70°C[a]	46%
4	$Pd(OAc)_2$	RuPhos	Br	toluene	1:1	13 h/ 100°C[a]	55%
5	$Pd(dppf)Cl_2$	-	I	toluene	1:1.5	16 h/ 110°C[a]	s.m.
6	Pd_2dba_3	SPhos	I	DMF	1:1.5	3 h/ 105°C[a]	deprot.
7	$Pd(OAc)_2$	SPhos	I	toluene	1:2	1.5 h / 120°C[a]	62%
8	$Pd(OAc)_2$	RuPhos	I	toluene	1:2	1.5 h / 120°C[a]	85%

s.m. = starting material; deprot. = deprotection; a = microwave irradiation.

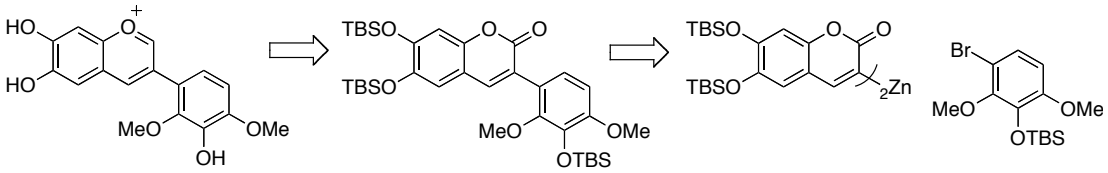
Table 5 – Optimization of the Suzuki cross-coupling.

The best result was obtained using palladium(II) acetate and Buchwald's RuPhos ligand[32] as catalyst system, in combination with toluene and dry potassium carbonate under microwave conditions at 120 °C.

It is noteworthy to mention, that coupling under standard conditions using aqueous media or aqueous bases in polar solvents lead to deprotection of the TBS ethers. This is probably due to the labile TBS-phenol bond, which can be easily deprotected under basic as well as acidic aqueous conditions. Another important lesson taught by this system is the acceleration of the cross-coupling reaction by microwave irradiation. This is believed to happen due to thermal effects. Homogeneous heating of polarized solvents increase the rates of formation of products, especially in transition metal catalysis.[33]

II. 1. 4. Negishi coupling approach

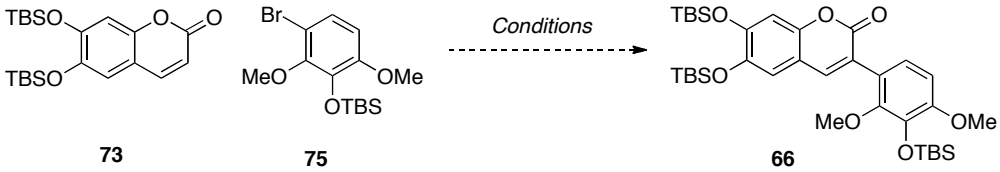
Suzuki cross-coupling approach worked well and gave access of TBS protected esculetin **73**. To minimize the step number, it was believed that zincated TBS-esculetin **77** could react further with aryl bromide **75** in a cross-coupling reaction using Negishi conditions (Scheme 30).



24 **66** **77** **75**

Scheme 30 – Retrosynthesis for the formation of the isoflavylium salt from coumarin *via* Negishi approach.

It is proven, that the TBS protected esculetin can be regioselectively metalated by zinc bases. Therefore the metalation by optimizing the system was tested with different literature known TMP-Zn derivatives (Table 6). [4, 34]



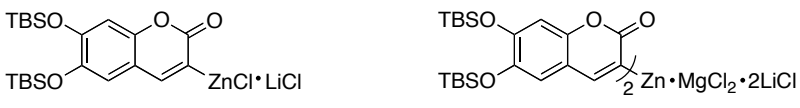
73 **75** **66**

Entry	Base	Catalyst	Ligand	Solvent	Ratio 73:75	Conditions	Yield
1	**78**	$Pd(PPh_3)_4$	-	THF/toluene	1:1	20 h/ 100°C	s.m.
2	**78**	$Pd(dppf)Cl_2$	-	THF	1:1	20 h/ 100°C	s.m.
3	**78**	PEPPSI-iPr	-	CH_2Cl_2	1:1	20 h/ 100°C	c.m.
4	**78**	$Pd(OAc)_2$	RuPhos	toluene	1:1.4	6 h/ 70°C	51 %
5	**78**	$Pd(OAc)_2$	XPhos	toluene	1:1	8 h/ 70°C	40 %
6	**78**	$Pd(OAc)_2$	SPhos	toluene	1:1	5 h/ 60°C	64 %
7	**78**	$Pd(OAc)_2$	SPhos	toluene	1.4:1	4 h/ 60°C	84 %
8	**79**	$Pd(PPh_3)_4$	-	toluene	1:1	20 h/100°C	s.m.
9	**79**	$Pd(OAc)_2$	RuPhos	toluene	1:1	7 h/80°C	45 %

s.m. = starting material; c.m. = complex mixture.

Table 6 – Optimization of the Negishi cross-coupling.

As shown aryl coumarin **66** can be obtained in very good yields using palladium(II) acetate and Buchwald's SPhos ligand[32] as the catalyst system and $TMP_2Zn{\bullet}MgCl_2{\bullet}2LiCl$ (**78**) as zinc base. TMPZnCl•LiCl (**79**) resulted in the same product, yet in lower yield, which might be due to the electronic reasons of the mono zincated species (Figure 7).

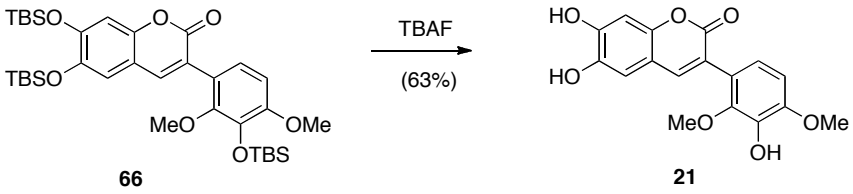


80 **81**

Figure 7 – Different metalated coumarins.

It is noteworthy to mention that, despite the argument that one coumarin of the diorganozinc species might act as a "dummy" ligand, both coumarin units couple in this reaction to give cross-coupled products. One of the major issues was the generation of homocoupled products. Due to the electron rich aromatic bromide, literature known second transmetalation processes can occur giving rise of the homocoupled products.[35] Therefore, an excess of coumarin **73** was used to suppress homocoupling to small amounts.

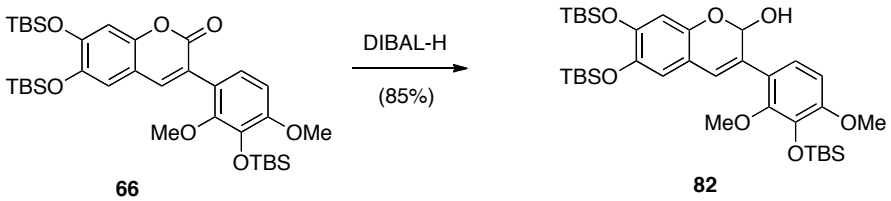
TBS deprotection resulted in the natural product santalin AC (**21**) (Scheme 31).[2]



66 **21**

Scheme 31 – Desilylation yielded in santalin AC.

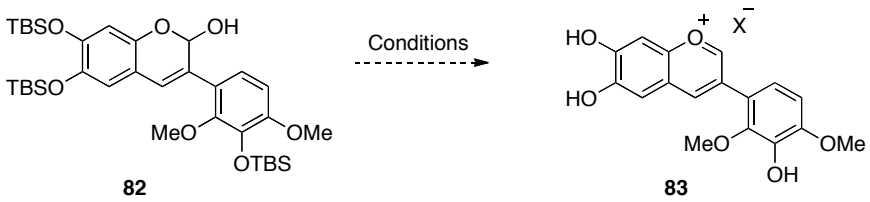
En route to isoflavylium salt, coumarin **66** was reduced to lactol **82** using DIBAL-H (Scheme 32). During the optimization studies it appeared that slow addition of the reducing agent as well as using on equivalent at very low temperature was crucial to avoid overeduction of the desired lactol, resulting in isoflavenes.



66 **82**

Scheme 32 – Reduction of coumarin to lactol **82**.

With lactol **66** in hand, the formation of isoflavylium salt **83** was attempted. A variety of strong acids that bear a non-nucleophilic counterion were tested making the salt isolable from acidic media (Table 7).[16b]



82 83

Entry	Brønstedt Acid	Solvent	Eq. (acid)	Yield
1	HCl	Et_2O	3	c.m.
2	HBF_4	AcOH	3	traces + c.m.
3	HPF_6	AcOH	3	traces + c.m.
4	$HClO_4$	AcOH	3	39 %
5	$HClO_4$	AcOH	5	76 %
6	$HClO_4$	AcOH	9	55 %

c.m. = complex mixture.

Table 7 – Optimization of the formation of isoflavylium salt.

The best results for the formation of the isoflavylium salt could be achieved by treating lactol **82** with perchloric acid in acetic acid. In this step, a subsequent protonation, dehydration and final global deprotection lead to isoflavylium perchlorate in one operation. Problematic isolation could be overcome by precipitation from acetic acid, which finally afforded crystals suitable for X-ray (Figure 8).

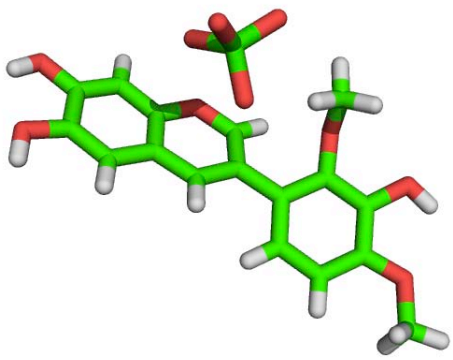
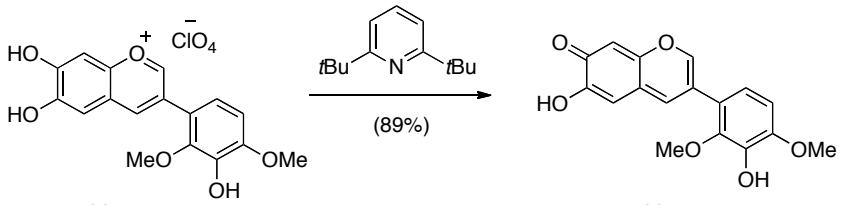


Figure 8 – Crystal structure of isoflavylium perchlorate **81**.

This structure is the first report of an isoflavylium salt bearing free hydroxy groups, while the perchlorate is hovering over the positively charged oxygen of the pyrylium moiety.

For the synthesis of further members of the santalin family it was important to deprotonate the rather acidic isoflavylium salt **81** to the corresponding anhydrobase **30** as can be seen in Scheme 33. Attempts with inorganic bases (e.g. NaOH, NaOAc, NaOMe, basic buffers) in aqueous media were unsuccessful. Finally the sterically demanding, non-nucleophilic base 2,6-*bis*-*tert*-butyl pyridine in acetonitrile gave anhydrobase, which could be isolated *via* precipitation.

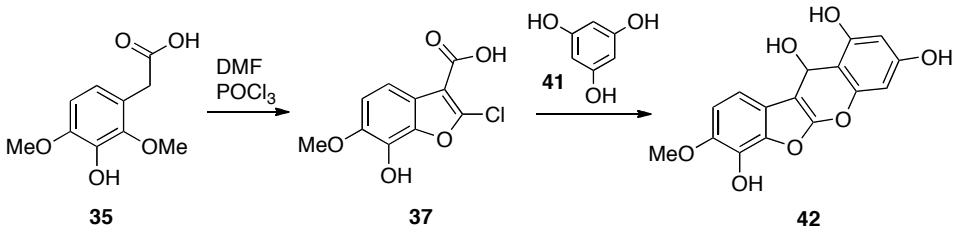


83 **30**

Scheme 33 – Deprotonation resulted in anhydrobase **30**.

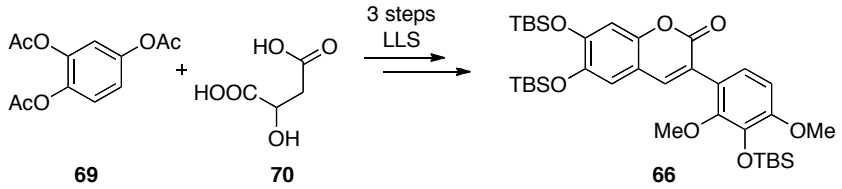
II. 1. 5. Summary

In summary, this chapter describes the successful preparation of anhydrobase **30**. Starting from classical approaches towards the anhydrobase synthetic surprises lead to an approach towards the natural product ayamenin E (**40**). A formal 3 + 3 cycloaddition resulted benzylic alcohol **42**, which so far could not be oxidized to ayamenin E (Scheme 34).



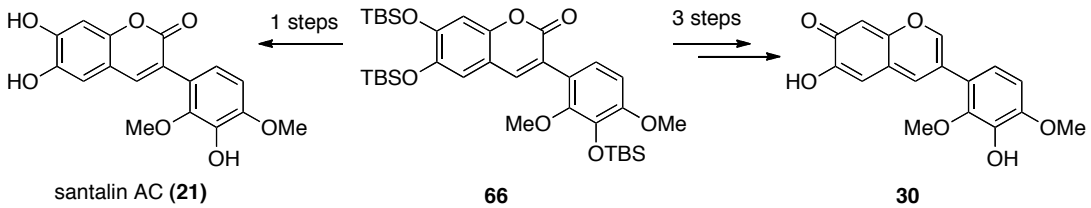
Scheme 34 – Synthesis of the reduced form of ayamenin E.

While this rapid protecting group free approach failed, different attempts were carried out, including a Knoevenagel coumarin synthesis and late stage functionalizations starting from protected esculetin using Suzuki and Negishi cross-couplings. A novel method developed by the group of Prof. Knochel lead to regioselective zincation and a subsequent Negishi cross-coupling resulted in coumarin **66** in only three steps (Scheme 35).



Scheme 35 – Rapid assembly of coumarin **66** using zinc mediated Negishi coupling.

Coumarin **66** is the branching point in the synthesis of all members of the santalin family. While deprotection lead to santalin AC (**21**), a reduction followed by dehydratisation and global deprotection and deprotonation resulted in anhydrobase **30**, the building block for all members of the santalin family (Scheme 36).

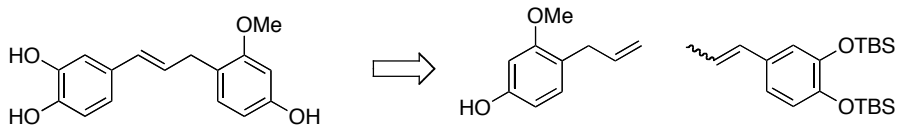


Scheme 36 – Coumarin **66** acts as a branching point for santalin AC **(21)** and anhydrobase **30**.

II. 2. Preparation of Benzylstyrene in the Synthesis of Santalin Y

For the distinct synthesis of members of the santalin family, a robust and selective synthesis of *trans*-benzylstyrenes had to be developed.

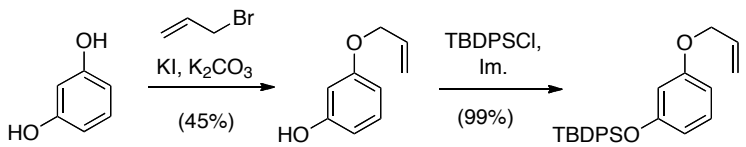
The attempts in this field were guided by literature precedence for the preparation of this neglected class of natural products using olefin cross-metathesis.[7b] Retrosynthetically, benzylstyrene **27** could be derived from allylphenol **84** and styrene **85** (Scheme 37).



27 **84** **85**

Scheme 37 – Retrosynthetic analysis for the generation of benzylstyrene **27**.

Lewis-acid were shown to promote aromatic Claisen rearrangements for the exact system, giving a fast entry to allylphenolic portion **84**.[36] The synthesis started with mono allyl protection of **86**, which gave the product **87** in moderate yields due to competing *bis*-allylation of resorcinol **86**. Selecting the appropriate protecting group for the remaining free phenol was crucial, due to its sterical influence in the regioselective outcome of the Claisen rearrangement (Scheme 38).

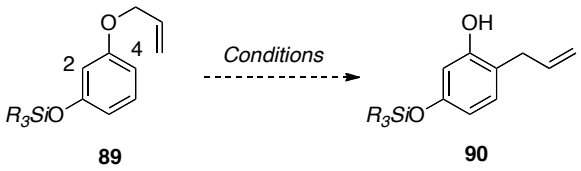


86 **87** **88**

Scheme 38 – Preparation of the Claisen rearrangement precursor.

The TBDPS protecting group is superior to the smaller TBS protecting groups, leading to a 11:1 (TBDPS) and a 7:1 (TBS) mixture of regioisomers favoring 4- over 2-allyl phenol (Table 8). It is remarkable that Lewis–acids promote the reaction at

low temperatures, given the fact that at standard conditions aromatic Claisen rearrangements can be observed at very high temperatures.[36]

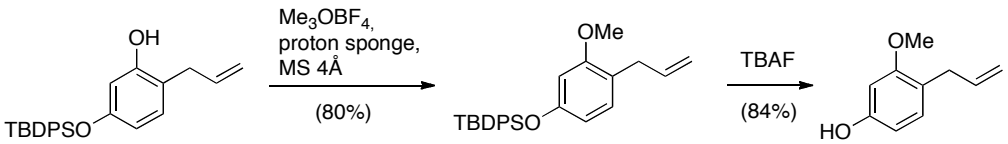


89 **90**

Entry	Catalyst	Solvent	Protecting group	Yield
1	BCl_3	CH_2Cl_2	TBS	45 %
2	$EtAlCl_2$	CH_2Cl_2	TBDPS	43 %
3	BCl_3	CH_2Cl_2	TBDPS	60 %
4	Et_2AlCl	CH_2Cl_2	TBS	59 %
5	Et_2AlCl	CH_2Cl_2	TBDPS	64 %

Table 8 – Optimization of the Claisen rearrangement.

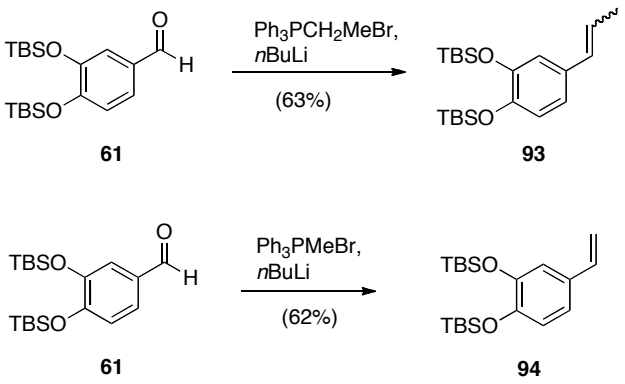
Methylation of the resulting phenolic group under mild conditions was carried out by treatment with Me_3OBF_4 in presence of proton sponge (Scheme 39).[37] Traditional conditions using bases and methyl iodide resulted in complex mixtures of various methylated and silylated products, suggesting that these conditions in polar solvent desilylate allyl phenol **91** easily. Final deprotection using TBAF yielded allyl phenol **84**.



91 **92** **84**

Scheme 39 – Methylation and deprotection yielding allyl phenol **84**.

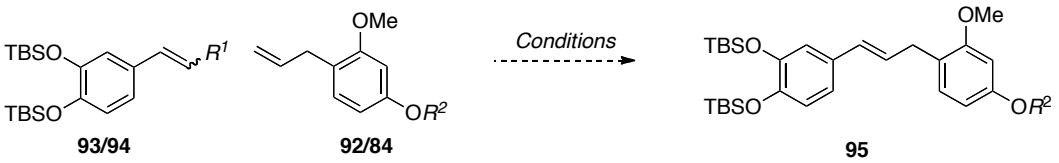
Wittig olefination of before mentioned benzaldehyde **61** afforded styrenes **93** and **94** in moderate yields (Scheme 40).



Scheme 40 – Preparation of styrene coupling partners using Wittig olefination.

Selectivity in cross-metathesis depends strongly on the olefinic coupling partners. Based on studies from Grubbs *et al.*, [7a] one can predict tendencies for hetero- and homocoupling based on classification of the olefinic building blocks. Therefore a methyl styrene **93** and a simple styrene **94** were used as olefins for the cross-metathesis to favor the formation of the desired hetero coupled product **95**.

The olefin cross-metathesis was attempted using either dichloromethane or toluene as solvent systems and ruthenium based metathesis catalysts (Table 9).



93/94 92/84 95

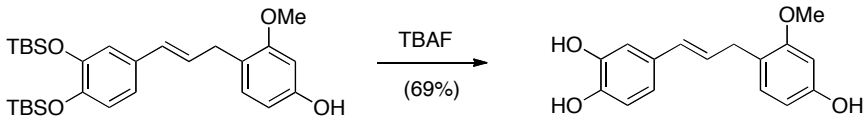
Entry	Catalyst	Solvent	R_1	R_2	Ratio 93/94:92/84	Yield
1	G I	CH_2Cl_2	Me	H	1:1	13 %
2	G II	CH_2Cl_2	Me	H	1:1	62 %
3	HG I	CH_2Cl_2	Me	H	1:1.5	17 %
4	HG II	CH_2Cl_2	Me	H	1:2	27 %
5	G II	toluene	H	H	1:1	56 %
6	G II	toluene	Me	TBDPS	1:1	n.i.

n.i. = not possible to isolate.

Table 9 – Optimization of olefin cross-metathesis.

Olefin cross-metathesis reaction worked best with dichloromethane and Grubbs 2nd generation catalyst. The best results were achieved with free allyl phenol and this substrate had the advantage of easier purification.

Final deprotection using TBAF resulted in benzylstyrene **27**, which can be directly used in the synthesis of santalins in the next step (Scheme 41).



96 27

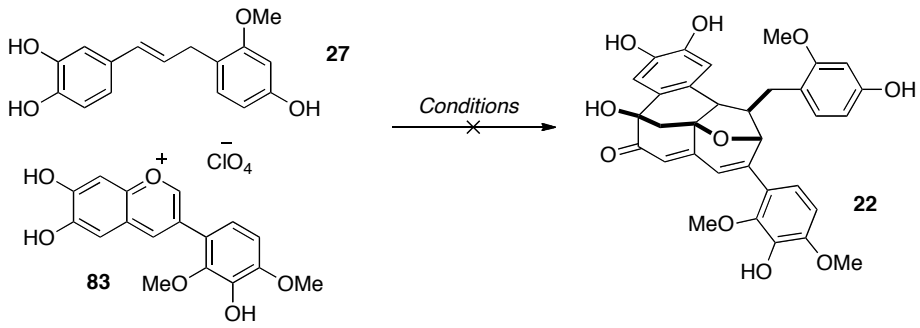
Scheme 41 – Final deprotection using the fluoride source TBAF.

In summary a short synthesis of benzylstyrene **27** has been accomplished in a longest linear sequence of 7 steps applying a Lewis–acid promoted aromatic Claisen reaction as well as an olefin cross-metathesis.

II. 3. Studies towards Santalin Y

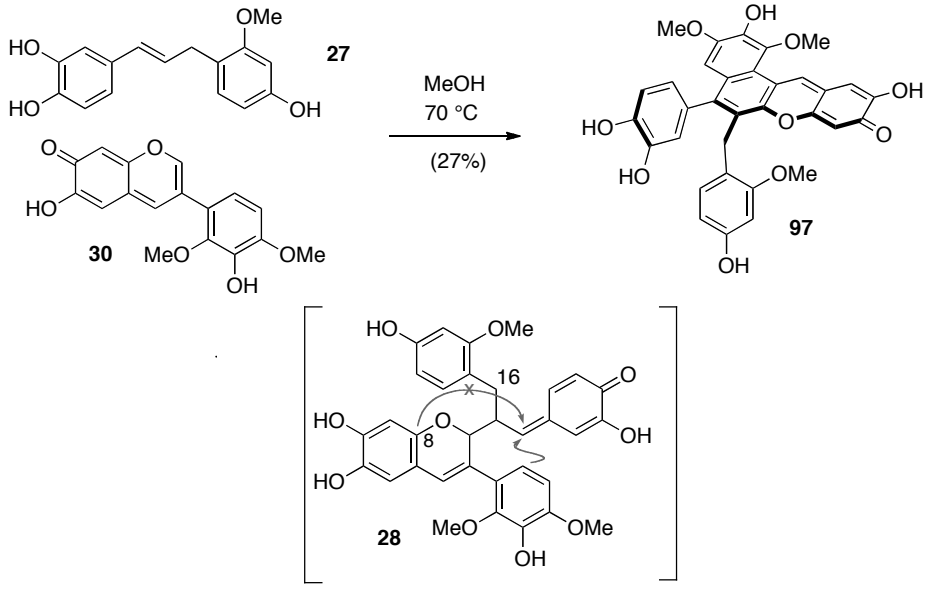
II. 3. 1. Thermal Coupling

With isoflavylium, anhydrobase and benzylstyrene in hand, the intermolecular coupling leading to santalin Y was investigated. A thermal reaction was envisaged resulting in santalin Y from isoflavylium to precursor **29**, which can react further to santalin Y in one step. When benzylstyrene **27** was reacted with isoflavylium perchlorate **83**, decomposition of **27** was observed, at low and high temperatures (Scheme 42). This is most likely attributed to the fact, that the isoflavylium perchlorate is very acidic due to the presence of perchloric acid. Strong acidic media might result in cationic polymerization of benzylstyrene **27** to polystyrenes.



Scheme 42 – Attempts towards santalin Y using isoflavylium perchlorate **83** were unsuccessful.

Therefore, the moderately basic anhydrobase **30** was employed and reacted in presence of benzylstyrene **27** at elevated temperatures. Under thermal conditions, santalin Y could not be obtained but only formation of benzoxanthenone structure **97** was observed. The main reason for selective generation of this structure is attributed to the electronrich and nucleophilic pyrogallol unit of the anhydrobase. The first step in this cascade is the nucleophilic attack of benzylstyrene **27** to anhydrobase **30** generating *para*-quinone methide **28**. This very electrophilic position is preferentially attacked by the less bulky and very nucleophilic pyrogallol unit instead of position 9 that would have led to santalin Y (depicted by arrows in Scheme 43).



Scheme 43 – Thermal coupling resulted in benzoxanthenone **97** and proposed transition state.

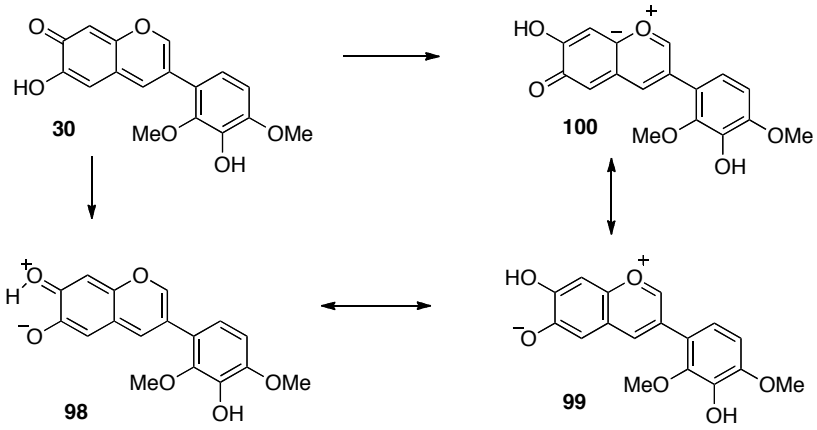
All attempts using thermal conditions and applying different additives (Lewis acids, Brønstedt acids) afforded benzoxanthenone structure **97**, called "santalin Y benzoxanthenone isomer". A potential thermal 1,3 hydride shift of benzylstyrene **27** leading to santalin A could be excluded, as the analytical data for isolated benzoxanthenone structure **97** did not match the reported data for the natural product (^{13}C NMR shift for C16 in ppm: 26.6 (**97**); 33.0 (santalin A)).[2] Subsequently further approaches to the synthesis of santalin Y were considered.

II. 3. 2. Photochemical Coupling

As thermal coupling pathways only lead to formation of "santalin Y benzoxanthenone isomer", optional biomimetic pathways leading to this complex natural product were investigated. Reaction pathways leading to reactive intermediates, facilitating a formal 1,3-dipolar cycloaddition were put focus on.

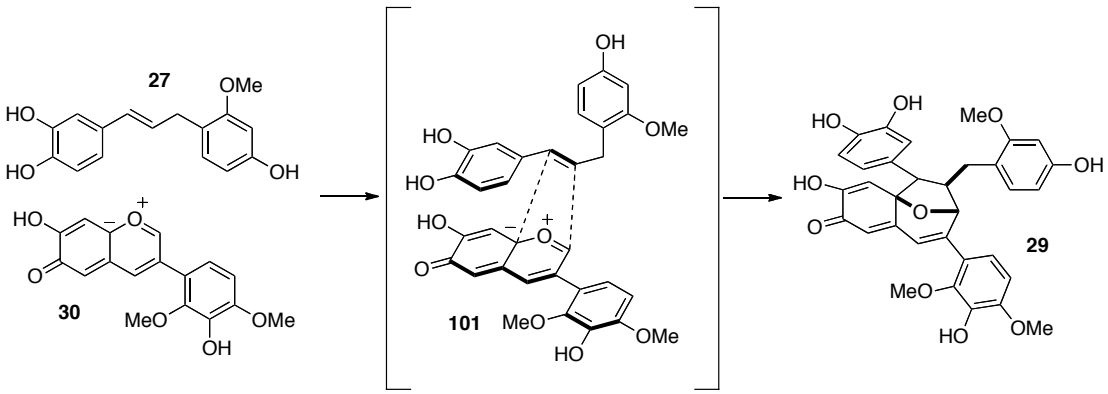
It was reported that hydroxy groups in close proximity to the carbonyl function might facilitate an excited state intramolecular proton transfer (ESIPT).[38] A proton,

interchelated between a hydroxy and a keto group might be transferred onto the carbonyl function upon irradiation with light. This mechanism would generate the zwitterionic molecule **98** (Scheme 44), which can be drawn in a tautomerized structure already displaying the electrophilic position next to the pyrylium oxygen and an *in situ* generated nucleophilic position in *para*-position to the phenolate **99**. This dipolar structure can be also drawn as a carbonyl ylide **100**, a well-known intermediate in 1,3-dipolar cycloadditions.



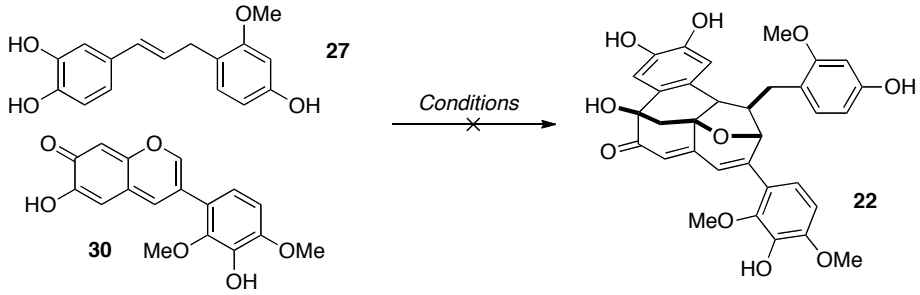
Scheme 44 – Proposed formation of 1,3 dipole by ESIPT.

Hypothetically, this dipolar structure can react further with olefinic structures. In this case, this olefin is benzylstyrene **27**, which could lead to structure **29** *via* the transition state depicted in Scheme 45. While 1,3-dipolar cycloadditions are described as concerted mechanisms, a stepwise process in the formation of the santalin Y precursor **29** might be more reasonable (Scheme 45).



Scheme 45 – Proposed cycloaddition with transition state for the formation of **29**.

This hypothesis has been used synthetically by different research groups to facilitate intra- and intermolecular cycloadditions leading to cycloheptanes with an oxa-bridge.[38a, 39] We investigated, whether this bioinspired plan could generate santalin Y using light and mild additives (Scheme 46). In opposition to previous examples, we hoped this pathway might provide the intermediate reacting further without use of protecting groups.



Scheme 46 – Attempts for the formation of santalin Y (**Table 10** with conditions in the experimental part).

Major experimental difficulties were faced due to the insolubility of anhydrobase **30** in most standard solvents used for photochemical reactions. It seemed that anhydrobase **30** is easily soluble in protic solvents, such as methanol, ethanol, and mixtures of organic solvents, e.g. acetone, acetonitrile, dichloromethane and chloroform with water. Anhydrobase could be dissolved in chloroform, but we were faced with solubility problems with benzylstyrene **27**. Carrying out the reaction in polar solvent led to preferential formation of side products resulting from the attack of

H_2O or *R*OH into the most electrophilic position of anhydrobase, leading to lactol or ketal **102**, respectively.

Even after extensive screening (Table 10) of different light sources the formal 1,3 dipolar cycloaddition could result neither in intermediate structure **29** nor santalin Y (**22**). One possible reason might be the absorption of light due to the coloring properties of anhydrobase in solution, which is at an absorption maximum of λ_{max} = 441 nm. We therefore tested different concentrations and different reaction vessels to provide a larger surface of irradiation. Unfortunately, this did not result in products **29** and **22**, but into formation of traces of benzoxanthenone **97** and its reduced precursor **103** (Figure 9). Generation of benzoxanthenone **97** and its precursor **103** are probably due to the thermal pathway. After long reaction time, anhydrobase **30** is attacked by benzylstyrene **27**, which can than be trapped by the electronrich and satirically less demanding pyrogallol unit. By exclusion of air, it was possible to isolate precursor **103**, which upon prolonged exposure to air oxidized to benzoxanthenone **97**.

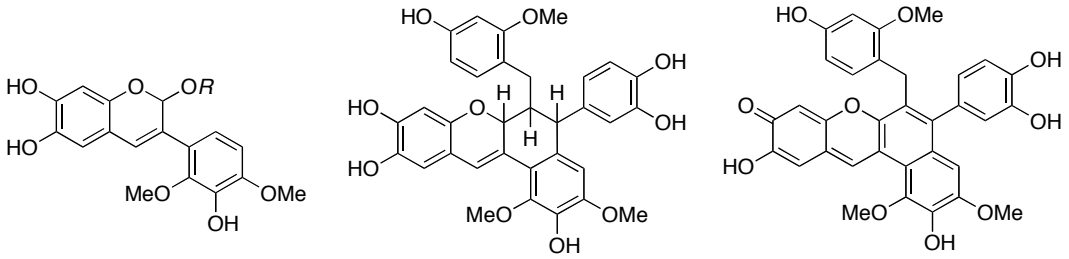
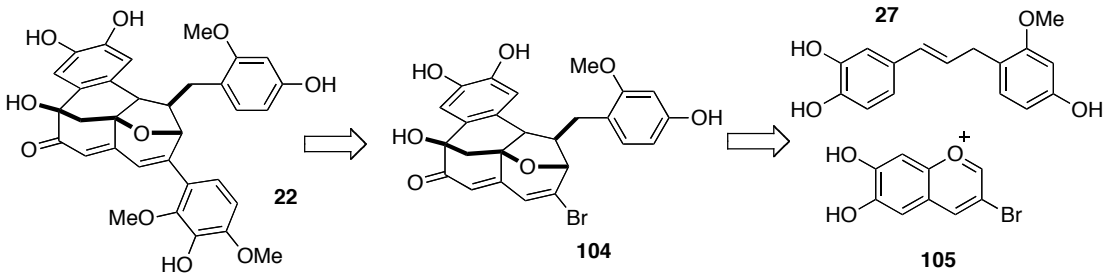


Figure 9 – Detectable side-products from photochemical attempts.

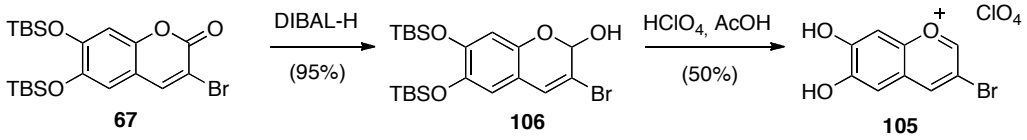
II. 3. 3. Late stage introduction of aryl ring

The very electron rich pyrogallol unit hampers the efforts towards the synthesis of santalin Y. So, it was decided to construct the oxafenestrane moiety first and introduce the aryl ring at a later stage, reacting bromoflavylium compound **105** with benzylstyrene **27** shown in Scheme 47, the reaction might lead to the tetracyclic core of santalin Y.



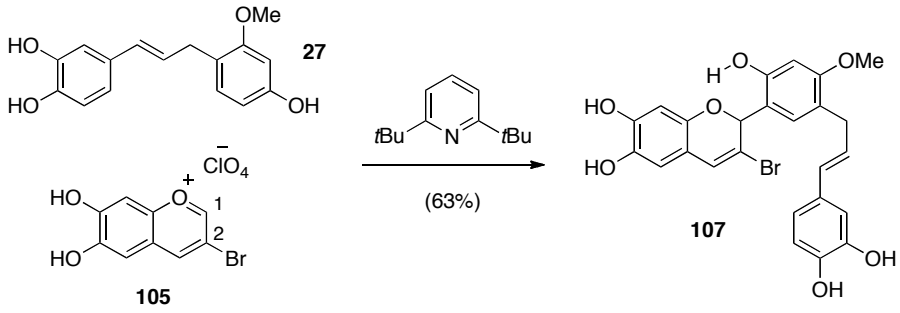
Scheme 47 – Retrosynthetic analysis by late stage arylation.

The synthesis started with the reduction of the previously prepared TBS bromo-esculetin **67** to the corresponding lactol **106** (Scheme 48). Using the same conditions as for lactol **106**, the yield improved drastically as no side-products were detected. Protonation, dehydration and deprotection could be achieved, but with slightly lower yields than in the arylated congener **82**.



Scheme 48 – Preparation of bromo flavylium perchlorate **105**.

With both coupling partners in hand, the investigation of thermal coupling by treating flavylium salt with base was started, in order to generate the anhydrobase *in situ* and adding benzylstyrene in one portion. Formation of oxafenestrane structure **104** could not be observed, but nucleophilic attack of the resorcinol moiety of benzylstyrene **27** to anhydrobase generated flavene **107** (Scheme 49).



Scheme 49 – Coupling resulted in flavene structure **107**.

From this result it is believed that an aryl substituent in C2 position is essential for favoring a vinyligous attack of benzylstyrene **27** to anhydrobase. In Figure 10 the left drawing describes the attack of the styrene group of benzylstyrene **27** to the anhydrobase **30**. This is favored over the attack of the resorcinol unit of benzylstyrene **27** shown by the dashed arrow, due to the minimal sterical interaction of the smaller styrene group with the pyrogallol unit next to C1. The right drawing describes the attack of the resorcinol unit to brominated anhydrobase **108**. This shows, that the resorcinol unit is the most nucleophilic position of the benzylstyrene if the sterical demanding pyrogallol unit is left out.

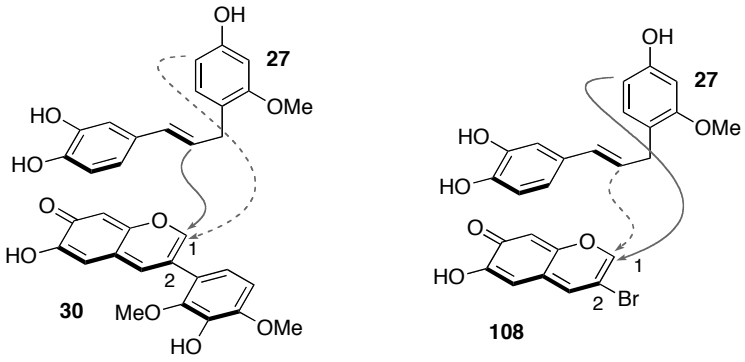
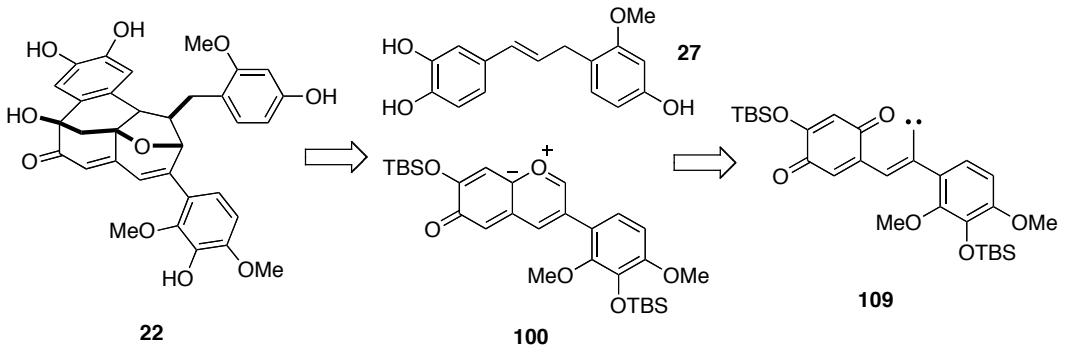


Figure 10 – Sterical hindrance favors the attack of the vinylogous attack.

II. 3. 4. Carbene generated carbonyl ylide coupling

Taking the previous results into account, we believed that generating the carbonyl ylide in presence of the pyrogallol unit is necessary in the synthesis of santalin Y. We

therefore came to the conclusion that by generating the reactive species **100** under thermal conditions santalin Y might be formed (Scheme 50).[40]



Scheme 50 – Retrosynthetic analysis generating carbonyl ylide from carbene.

Amino aziridine derivatives **110** and **111** (Figure 11) investigated by A. Eschenmoser could fragment with subsequent extrusion of nitrogen to afford a reactive carbene under thermal conditions.[41]

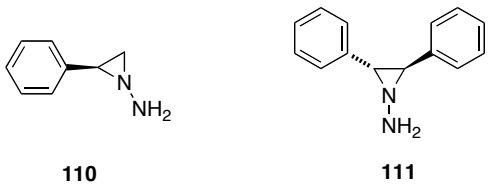


Figure 11 – Amino aziridines investigated by A. Eschenmoser.

Both known aminoaziridines **110** and **111** were prepared and the structure of **111** was confirmed by crystallographic analysis (Figure 12). During their preparation it was found out that diphenyl amino aziridine **111** has a higher tendency to decompose than compound **110**, probably due to the higher stability of stilbene **114** in comparison to the high ring tension of aziridines.

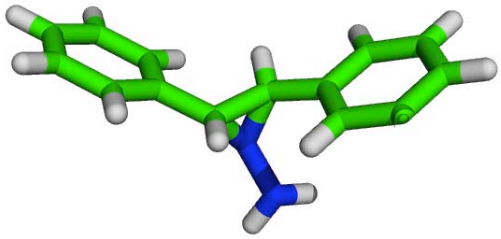
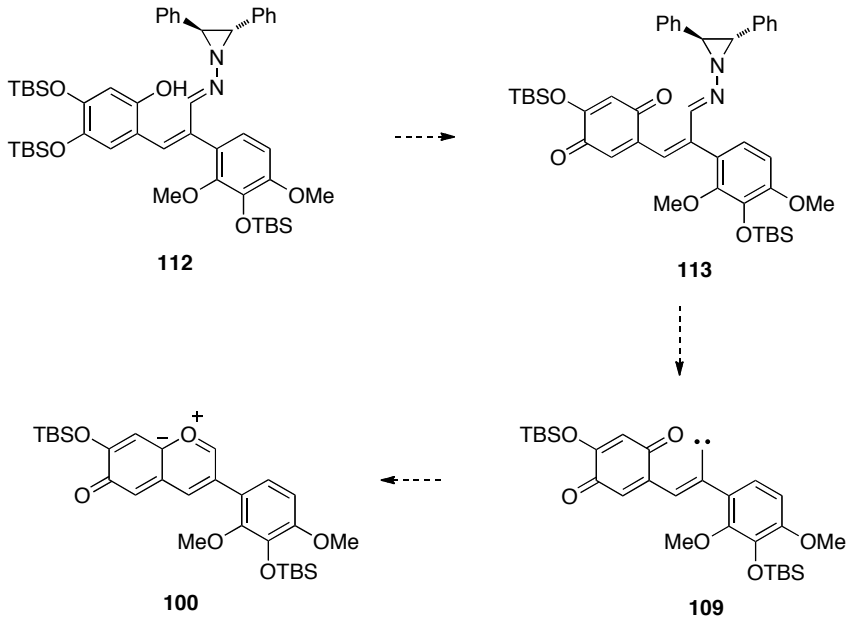


Figure 12 – Crystal structure of diphenyl amino aziridine **111**.

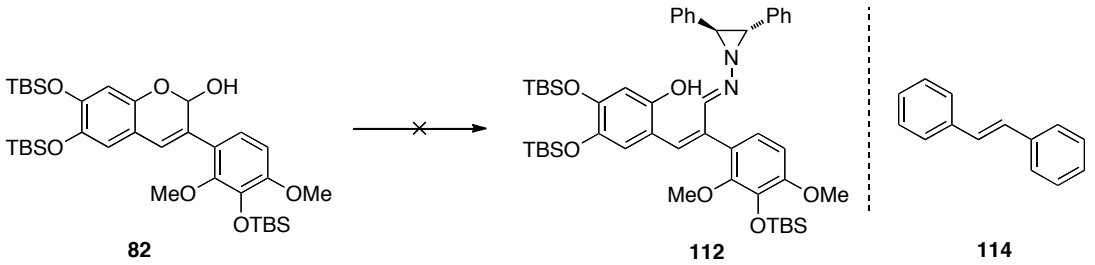
The synthesis started by treating the already prepared lactol **82** with amino aziridines **110** and **111**. That reaction should lead to phenol compound **112**, which upon desilylative quinone oxidation would lead to *para*-quinone **113**. Heating this compound would generate carbene **104** by extruding nitrogen and stilbene. Carbene could be nucleophilically attacked by quinone oxygen generating the carbonyl ylide **100** (Scheme 51).



Scheme 51 – Proposed formation of carbonyl ylide from carbene **109**.

During these studies it was found out that the coupling of amino aziridines **110** and **111** with lactol led to decomposition, yielding either complex mixtures of

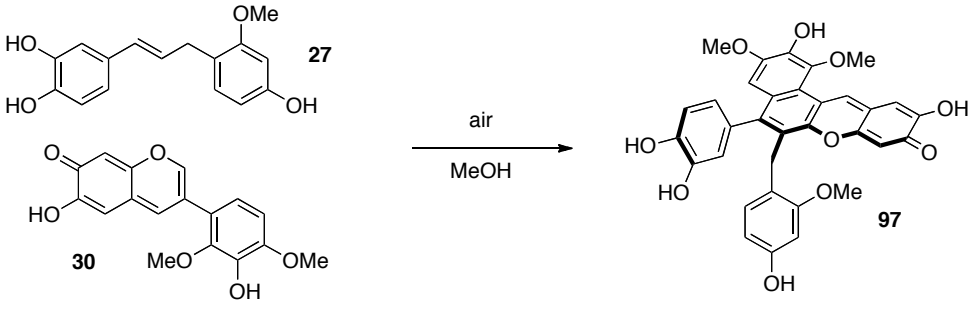
isoflavylium salts or stilbene **114**. The presence of acids or protic solvents increased the decomposition rate of amino aziridines **110** and **111** (Scheme 52).



Scheme 52 – Unsuccessful attempts to couple amino aziridines to lactol **82** and observation of stilbene **114**, the only detectable side-product.

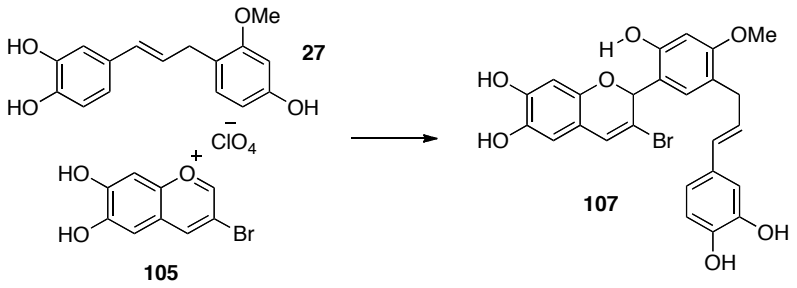
II. 3. 5. Summary

In summary, this chapter describes the progress towards the synthesis of santalin Y. Thermal coupling of deprotected benzylstyrene **27** and anhydrobase **30** afforded exclusively benzoxanthenone structure **97**. Attempts towards the oxafenestrane structure of santalin Y using "biomimetic conditions", for example thermal and photochemical approaches, resulted in structure **97** and its reduced precursor when experiments were attempted with inert conditions.



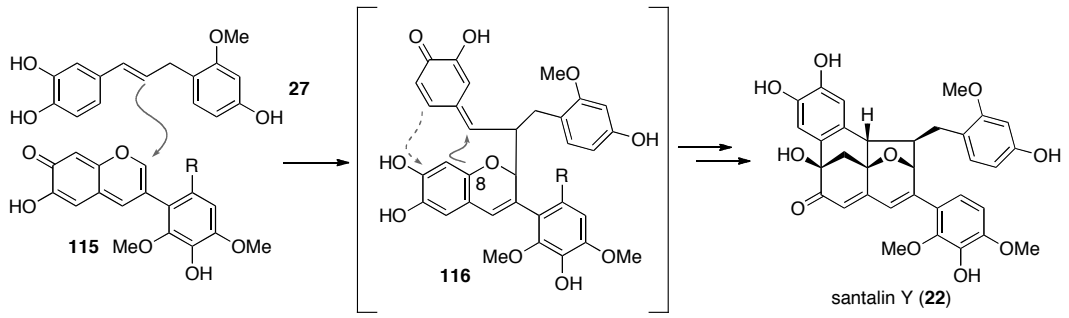
Scheme 53 – Thermal coupling of benzylstyrene **27** and anhydrobase **30** resulting in the benzoxanthenone structure **97**.

Coupling of a simplified benzopyrylium salt **105** and benzylstyrene **27** resulted in flavene structure **107**. This gave the insight that an aryl ring in the C2 position is essential in the regioselective coupling of benzylstyrene **27** to anhydrobase **30** due to steric reasons (Scheme 54).



Scheme 54 – Coupling of benzylstyrene **27** and anhydrobase **30** resulting in flavene **107**.

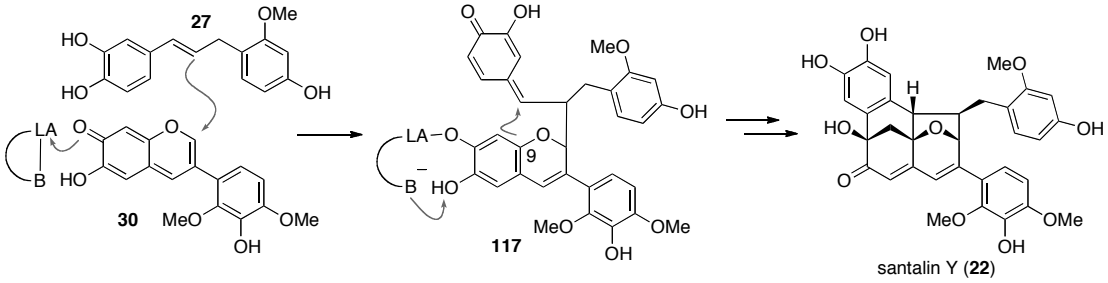
Future directions towards santalin Y may lead to two different approaches. The first approach includes blocking the nucleophilic pyrogallol unit by group *R* (**115**) (R = Br, TMS), thus favoring the nucleophilic attack of C8 to *para*-quinone methide **116**. This plan could potentially lead to santalin Y (**22**) after attack *via* the dashed arrow and removal of the blocking group (Scheme 55).



Scheme 55 – Future directions leading to santalin Y (R = blocking group).

A second approach involves cooperative dual catalysis, having a Lewis acidic (LA) and a Brønstedt basic site (B) incorporated in one catalyst, which is depicted in Scheme 56. The Lewis acidic moiety could potentially activate anhydrobase **30** favoring the nucleophilic attack of benzylstyrene **27**. The released basic portion could

then deprotonate the vicinal hydroxy group thus generating a nucleophilic position *para* to phenolate, which could attack *para*-quinone methide **117**. Subsequent Friedel-Crafts cyclization could be favored by the Lewis acid and generate santalin Y (**22**) in one step.



Scheme 56 – Future directions leading to santalin Y *via* dual catalysis.

Cooperative dual catalysts may be either metalorganic catalysts or organocatalysts. Lanthanide metalorganic catalyst **118** developed in the group of Shibasaki[42] display a Lewis acidic site, which upon coordination release a Brønstedt basic site (depicted in Figure 13). Thiourea based catalysts **119** developed from Takamoto[43] can activate carbonyls *via* H-bond donation and can subsequently deprotonate with an amine in close proximity. Due to the racemic nature of santalin Y an asymmetric induction by chiral ligands is irrelevant.

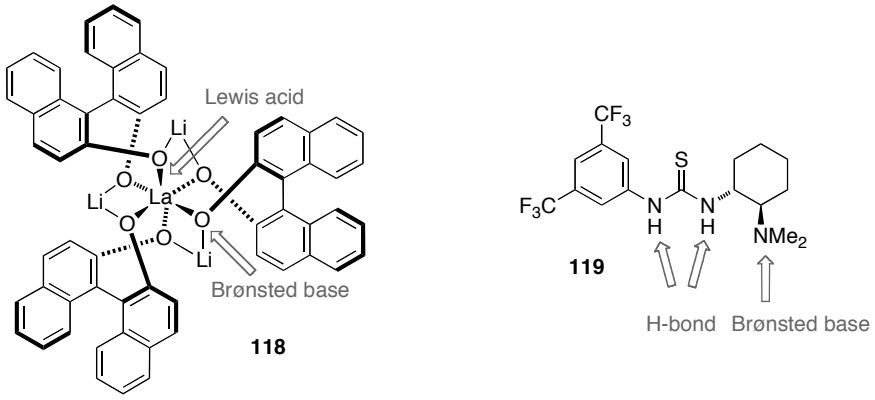


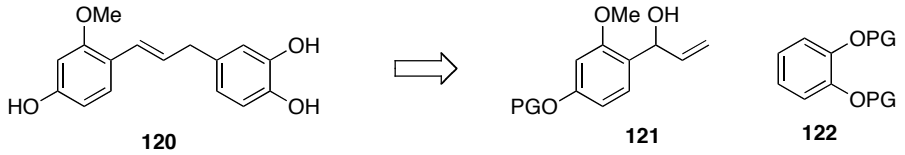
Figure 13 – Cooperative dual catalysts from Shibasaki **118** and Takamoto **119**.

III. Total Synthesis of Santalin A/B and Santarubin A/B

III. 1. Synthesis of Santalin A and B

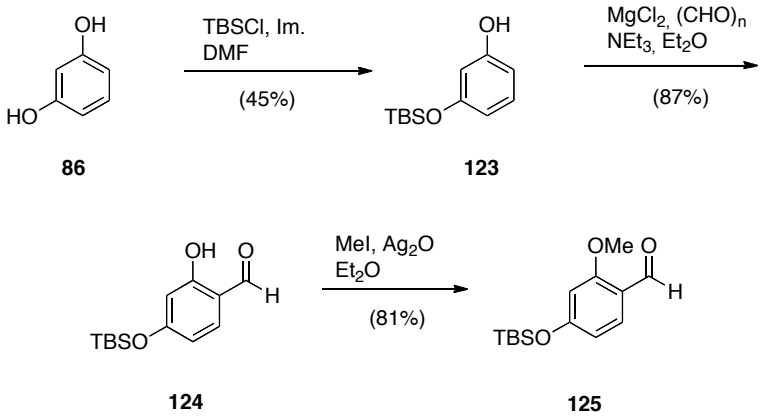
III. 1. 1. Synthesis of benzylstyrenes by Lewis-acid catalyzed allylation

The synthesis of benzylstyrenes was achieved using different strategies. A method described by the groups of Tamaru[44] and Chan[6], facilitating the formation of allylic cations from alcohols was examined, because these reactive intermediates can react further in a Friedel-Crafts type reaction to yield benzylstyrenes (Scheme 57). This can be achieved using Lewis- or Brønstedt-acids. In this approach the use of Brønstedt acids was avoided due to the instability of phenolic TBS groups to acidic conditions.



Scheme 57 – Retrosynthesis of benzylstyrene **120** using Friedel-Crafts allylation.

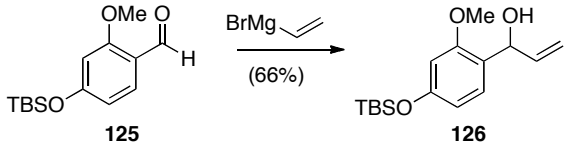
Synthesis of an allylic alcohol **121** started with monoprotection of resorcinol (**86**) to mono silyl ether **123**.[45] The product was obtained in moderate yields due to mixtures of mono- and di-protected resorcinol along with starting material. Selective *ortho*-formylation to benzaldehyde **124** was carried out under literature known conditions.[28] Successive methylation of benzaldehyde **124** to methyl ether **125** could be achieved using MeI and an excess of silver(II) oxide (Scheme 58).



86 **123** **124** **125**

Scheme 58 – Preparation of benzaldehyde **125**.

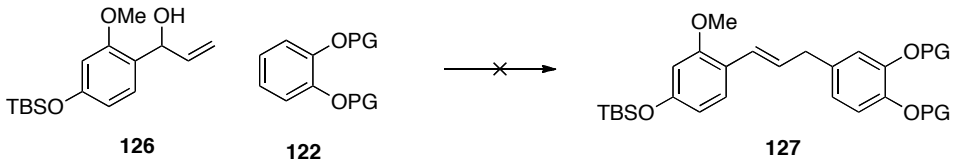
Addition of vinyl Grignard to benzaldehyde **125** resulted the desired **126** product in moderate yields (Scheme 59). The moderate yield can be explained by the sterical demanding *ortho*-methoxy group. This group might push the formyl group out of conjugation, thus making it less reactive.



125 **126**

Scheme 59 – Formation of allylic alcohol using vinyl Grignard.

With the allylic alcohol in hand, the Friedel-Crafts type reaction using different catalysts was tested. As depicted in Scheme 60, TBS protected catechol and catechol (**122**) were tested as nucleophiles with a variety of Lewis- and Brønstedt-acids.[6]



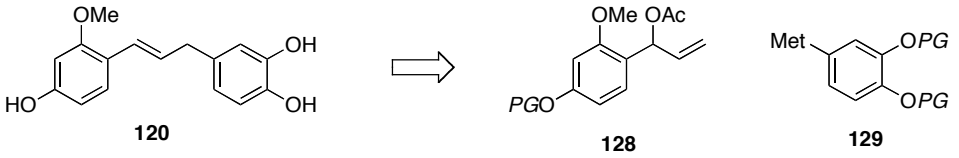
126 **122** **127**

Scheme 60 – Attempts of Friedel-Crafts allylation using catechol (PG = H, TBS).

Under various conditions the reaction did not provide the desired product **120**. The nucleophilicity of catechol derivatives does not appear to be strong enough in this reaction. Consumption of allylic alcohol leads to a complex, polar mixture. Catechol nucleophiles remain untouched in the reaction mixture, suggesting an allylic polymerization with the resorcinol moiety.

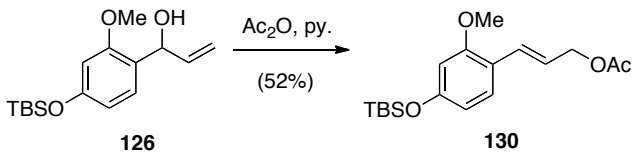
III. 1. 2. Synthesis of benzylstyrenes by Tsuji-Trost type allylation

Weak nucleophilicity of catechol derivatives seemed to hamper the previously described Friedel-Crafts reaction. Therefore, this reaction was conducted with more nucleophilic metal catechol derivatives and using an allylic ester, which can easily form an allylic cation in the presence of transition metals (Scheme 61).[44, 46]



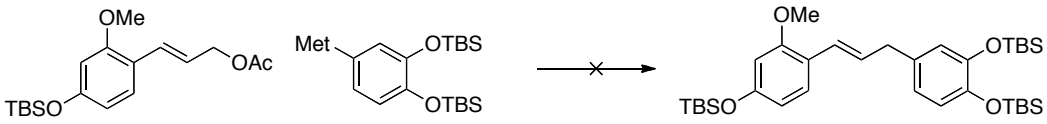
Scheme 61 – Retrosynthesis of benzylstyrene using Tsuji-Trost allylation or allylic arylation.

Therefore, the already prepared allylic alcohol **126** was converted into the corresponding allylic ester **130**. This reaction transposed the allylic pattern to the terminal allylic position, as can be seen in Scheme 62. The reason for this transposition might be the sterical demanding *ortho*-methoxy group.



Scheme 62 – Unexpected formation of allyl ester.

The prepared allylic ester **130** was used with a variety of different *in situ* generated metalated catechol species. The organometalic was generated using halogen-lithium-exchange and transmetallated to more covalent magnesium, zinc and tin species. Reacting this species further in presence of allylic ester and palladium(0) did not result in the desired benzylstyrene **132**. Dehalogenated catechol starting material was isolated, while the allylic ester **130** decomposed under these conditions (Scheme 63).

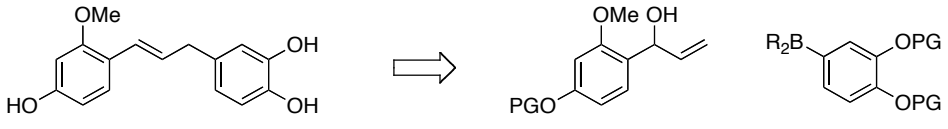


130 **131** **132**

Scheme 63 – Unsuccessful attempts of nucleophilic arylation.

III. 1. 3. Synthesis of benzylstyrenes by π-allyl-Suzuki cross-coupling

To test whether Tsuji-Trost type reactions work with organometals, the more stable, isolable organometalic species was used to prove their generation. Allylic alcohol **126** was reacted with boronic acid derivatives. This reaction has the advantage that under these conditions the boronic acid could activate allylic alcohol *in situ*, forming the allyl cation in presence of palladium(0) and couple the most nucleophilic, activated carbon in the same step (Scheme 64).[5]

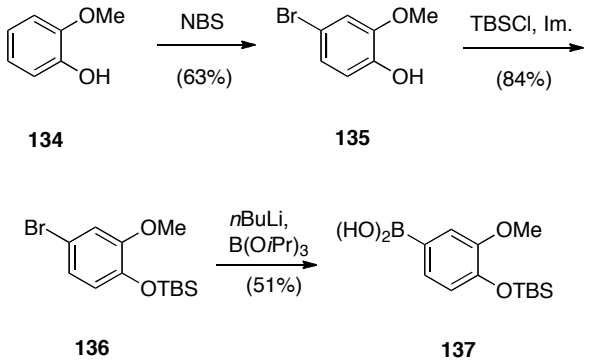


120 **126** **133**

Scheme 64 – Retrosynthesis of benzylstyrene using π-allyl Suzuki coupling.

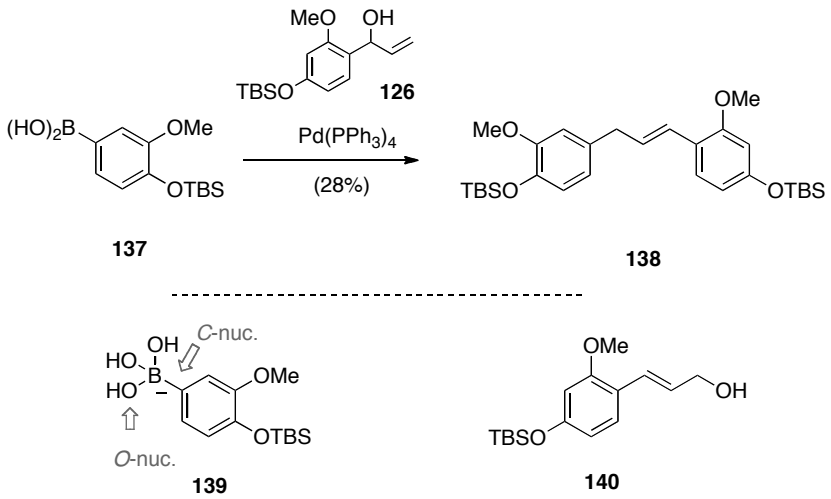
We planned to carry out this reaction for the benzylstyrenes, ultimately leading to santalin B, using guaiacol (**134**). Guaiacol **134** was selectively brominated in *para*-position to the free hydroxy group. Subsequent TBS protection yielded bromo guaiacol **135** in good yield. Bromine-lithium exchange, trapping with $B(OiPr)_3$ and

hydrolysis resulted in boronic acid **137** in moderate yield (Scheme 65). The moderate yield is due to competing spontaneous phenol formation.



Scheme 65 – Preparation of boronic acid **137**.

With the two coupling partners in hand, the π-allyl Suzuki cross-coupling was leading to successful formation of benzylstyrene **138** (Scheme 66).

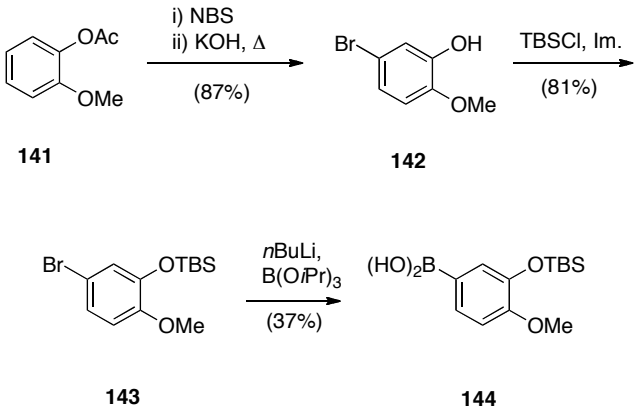


Scheme 66 – π-Allyl Suzuki coupling resulting in santalin B building block **138** and the intermediate borate **139** with the observed side-product **140**.

The generation of borate **139** in this reaction leads to both a carbon and oxygen nucleophile with competing reactivity, which is depicted in Scheme 66. The major side product was the known transposition of the allylic alcohol *via* attack of the

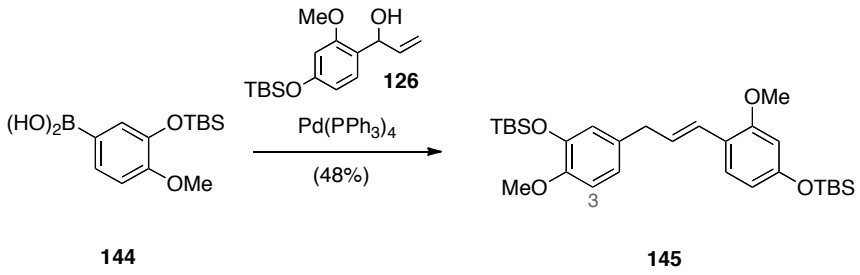
oxygen nucleophile to the terminal position, giving allylic alcohol **140**.[47] Even elevated temperatures and longer reaction time could not increase the yield.

Benzylstyrene **138** was reacted with anhydrobase **30** to santalin B (**18**) after deprotection (reaction is described in chapter III.1.5). Due to a shifted signal in ^{1}H NMR (position 30: 6.51 ppm (synthetic); 6.36 ppm (reported)) it was believed that bromination lead to the *meta*-bromination with respect to the TBS ether. Therefore the system was tested with boronic acid derived from a different brominated guaiacol as well. Preparation of boronic acid **144** started with selective bromination of acetoxy guaiacol **141** and subsequent saponification giving bromo guaiacol **142**. **142** was converted to silylated species **143** and bromine-lithium exchange, trapping with $B(OiPr)_3$ and hydrolysis yielded boronic acid **144** in moderate yield (Scheme 67).



Scheme 67 – Preparation of boronic acid **144** for iso-santalin B benzylstyrene.

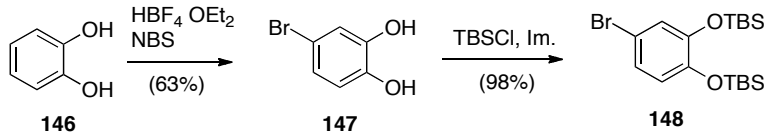
Palladium catalyzed coupling lead to benzylstyrene **145**, which is an isomer to **138** with respect to the position of the *O*-methyl group on the catechol moiety. This became clear after checking the final product with NOESY, which showed strong coupling from the methoxy group to C3 depicted in Scheme 68. Surprisingly, the yields were significantly higher owing to the increasing nucleophilicity of the carbon in *para*-position to the methoxy group.



Scheme 68 – π-Allyl Suzuki coupling resulting in iso-santalin B building block.

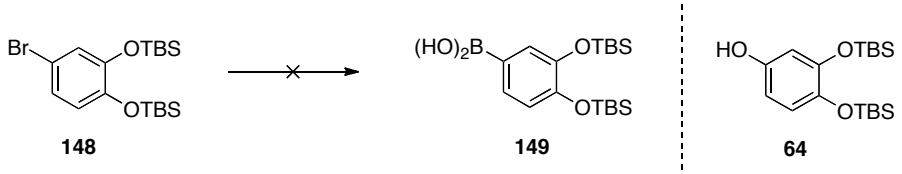
In this case, the major side product appeared to be also transposed allylic alcohol **140**, which could be isolated from the reaction mixture.

With these encouraging results in hand, this reaction with the symmetric catechol unit leading to the santalin A benzylstyrene was attempted. The synthesis started with bromination of catechol **(146)** under acidic conditions followed by double TBS-protection giving bromo catechol **147** in good overall yield (Scheme 69).



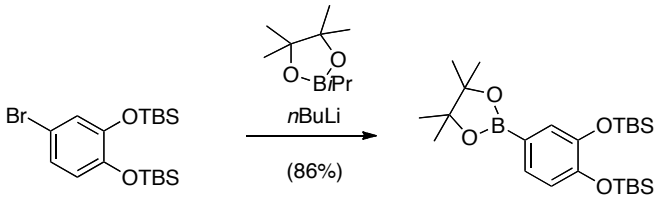
Scheme 69 – Preparation of TBS bromo catechol **148** suitable for the synthesis of santalin A.

Unfortunately, bromine-lithium exchange of **148** failed under various conditions only affording phenol **64** depicted in Scheme 70. This might be due to contamination of HCl in the hydrolysis step of boronic esters.



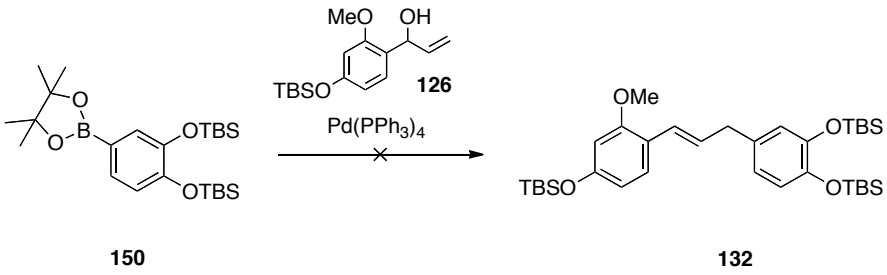
Scheme 70 – Attempts towards boronic acid **149** and only observed product phenol **64**.

Therefore, pinacol boronic ester was chosen as a substitute. This substrate should avoid side-reactions in the palladium catalyzed coupling step due to steric bulk, making the oxygen nucleophile less accessible. Indeed, pinacol boronic ester **150** could be formed in very good yield from TBS bromo catechol **148** *via* bromine-lithium exchange (Scheme 71).



Scheme 71 – Preparation of pinacol boronic ester **150**.

Unfortunately, the subsequent coupling step to benzylstyrene **132** failed under various conditions using different palladium catalysts, solvents and microwave irradiation (Scheme 72). This might be due to the lower nucleophilicity of pinacol boronic esters.

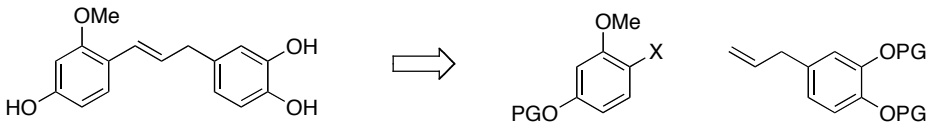


Scheme 72 – Coupling of pinacol boronic ester went uneventful.

III. 1. 4. Synthesis of benzylstyrenes by Heck cross-coupling

It appeared that the major problem in the synthesis of benzylstyrene **132** was the catechol unit or the functionalization thereof. We planned to use resorcinol halides **151** to react with a catechol allylspecies **152** in a palladium(0) catalyzed Heck cross-coupling.[48] Possible concerns, as for example the selective elimination of the

palladium species could be overcome by literature known additives.[48] The retrosynthesis is shown in Scheme 73.

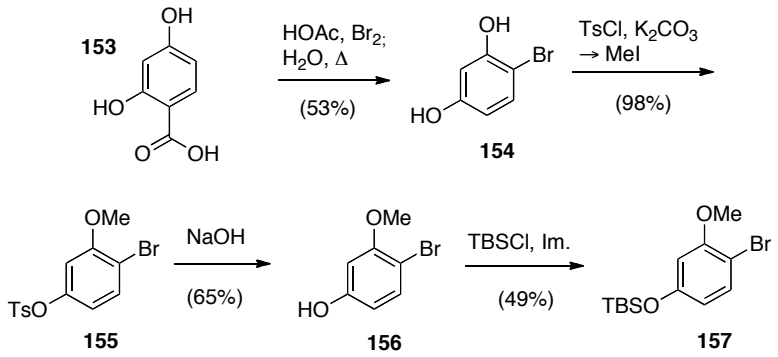


120 **151** **152**

Scheme 73 – Retrosynthesis of benzylstyrene using Heck cross-coupling.

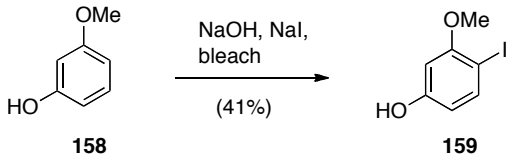
The synthesis started with the preparation of resorcinol halides. We therefore chose aryl iodides and aryl bromides due to their known reactivity in oxidative additions with palladium.

For the selective introduction of bromide in methyl resorcinol, a literature known procedure to resorcinol bromide **156** was followed.[49] Thus bromination of resorcylic acid **153** with subsequent decarboxylation at elevated temperatures gave **154**, which upon selective tosylation of resorcinol followed by methylation of the *ortho*-phenolic group resulted in protected aryl bromide **155**. Deprotection of the tosyl group under basic conditions resulted in deprotected phenol **156**, which could be silylated in moderate yield. This 4-step sequence gave selective entry to bromide coupling partner **157** in good overall yield (Scheme 74).



Scheme 74 – Formation of aryl bromide **157**, precursor for the Heck reaction.

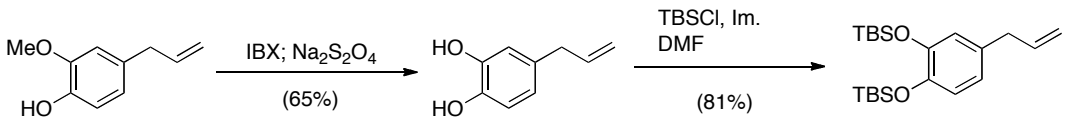
Selective iodination was accessible from commercially available mono methoxy resorcinol **158** by oxidative iodination to afford iodo resorcinol **159** in moderate yield (Scheme 75).



158 **159**

Scheme 75 – Regioselective iodination of phenol **158**.

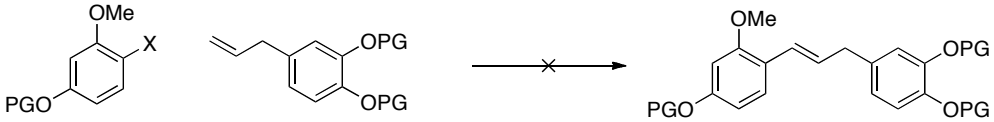
The allylic coupling partner **152** was prepared from commercially available eugenol (**160**) by oxidative demethylation *via* the *ortho*-quinone. Reduction with $Na_2S_2O_4$ in the same operation yielded allyl catechol **161** (Scheme 76). TBS protection resulted in the formation of allyl coupling partner **162** in good yields.[50]



160 **161** **162**

Scheme 76 – Oxidative demethylation of eugenol resulted in allylcatechol **162**.

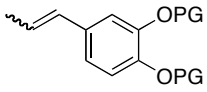
This reaction was tested under various conditions, applying different solvents, palladium sources and different coupling partners. Unfortunately, formation of benzylstyrene **163** could not be observed under any conditions (Scheme 77).



151 **152** **163**

Scheme 77 – Unsuccessful attempts of the Heck coupling (PG = H, TBS; X = Br, I).

Under the applied conditions, most of the time TBS deprotection could be observed, which was due to polar solvents like DMF or solvent mixtures with water. In two cases, the isomerization of the double bond of allylspecies **152** could be observed giving traces of styrene **164** (Figure 14).

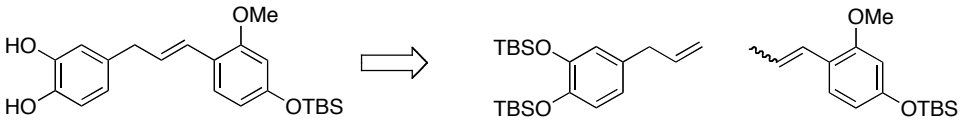


164

Figure 14 – Isomerized product from Heck coupling.

III. 1. 5. Synthesis of benzylstyrenes by cross-metathesis and biomimetic synthesis of Santalin A/B

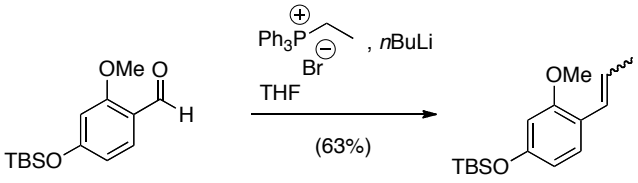
The successful experience with olefin cross-metathesis in the synthesis of benzylstyrene **27** suitable for santalin Y prompted us to test the same reaction conditions with different allyl species **162** and benzylstyrene **165** (Scheme 78).[7]



120 **162** **165**

Scheme 78 – Retrosynthesis of santalin A benzylstyrene **132** using olefin-metathesis.

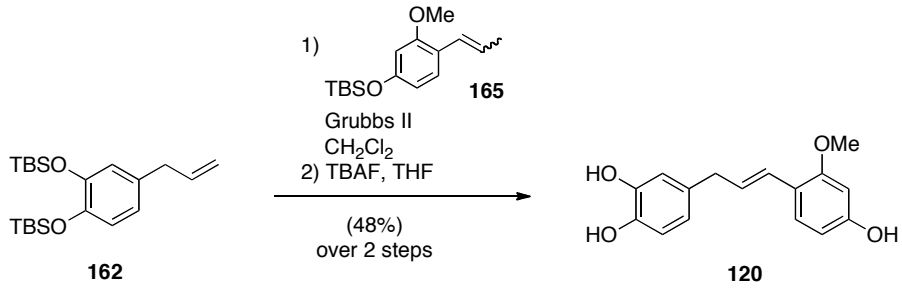
Styrene coupling partner **165** was prepared from benzaldehyde **125** under Wittig conditions in good yields (Scheme 79).



125 **165**

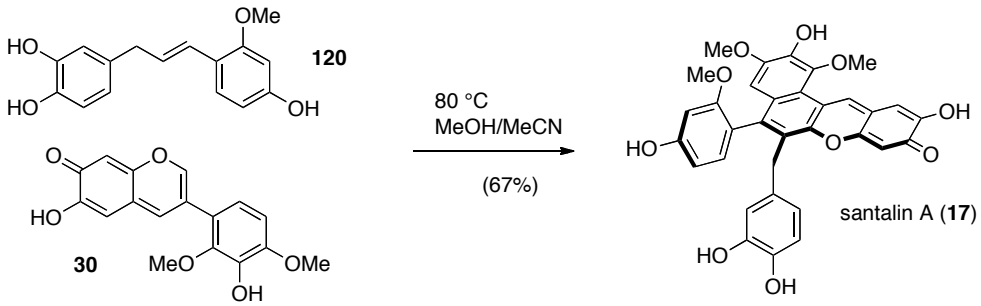
Scheme 79 – Styrene coupling partner **165** was prepared from benzaldehyde **125**.

The olefin cross-metathesis resulted in benzylstyrene **132**, which could not be characterized due to co-polar impurities. Deprotection with a fluoride source resulted in pure benzylstyrene **120** in moderate yield (Scheme 80).



Scheme 80 – Olefin cross-metathesis to form benzylstyrene **120**.

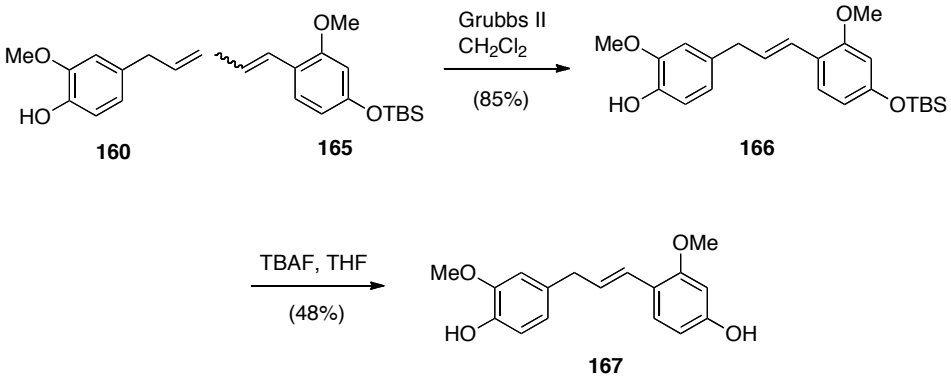
With the two coupling partners in hand, conditions were applied which have been already investigated in the previous chapter. With slight modifications, e.g. using a solvent mixture of MeCN and MeOH, it was able to isolate santalin A in good yields (Scheme 81), given the complexity of the proposed cascade. Best results were obtained with a solvent mixture of methanol and acetonitrile, under air atmosphere, at elevated temperatures. During the studies towards santalin A it was realized that an excess of anhydrobase **30** (2.5 eq.) was necessary for the full conversion. This arises the question whether **30** only plays a role as an electrophile or can act as an internal oxidant as well.



Scheme 81 – Biomimetic cascade resulting in santalin A.

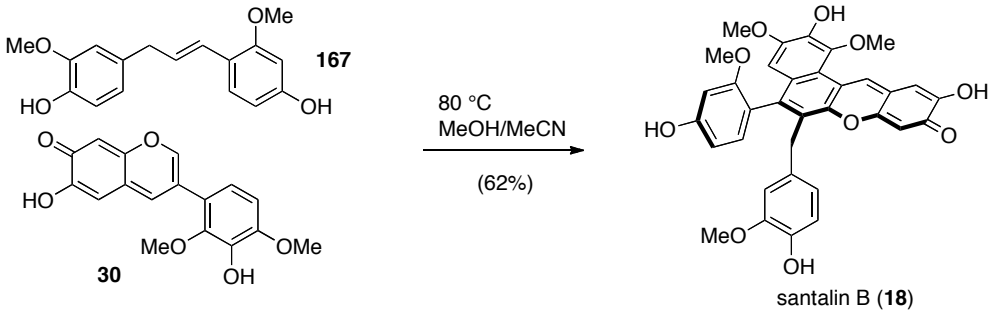
For the synthesis of santalin B, coupling partner **167** was prepared, also using olefin cross-metathesis. Commercially available eugenol (**160**) and styrene **165** were used in

the formation of benzylstyrene **166**. Due to the difference in polarity, benzylstyrene could be separated from its homo-coupled side products by flash column chromatography. Deprotection of the TBS-ether using TBAF resulted in benzylstyrene **167** in moderate yields, resulting in coupling partner **167** in a longest linear sequence of six steps from commercially available material (Scheme 82).



Scheme 82 – Olefin cross-metathesis resulted in desired santalin B benzylstyrene **167**.

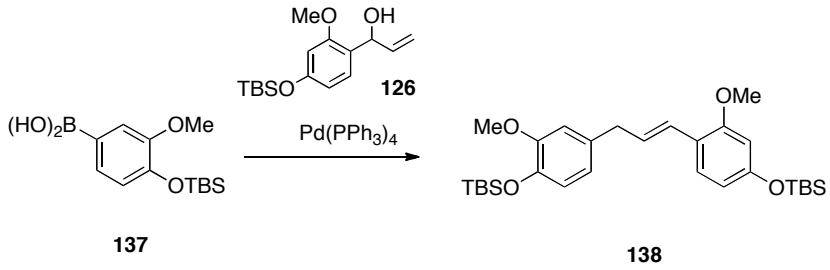
Synthesis of santalin B was accomplished, applying the same conditions used for santalin A (Scheme 83). While santalin A precipitated upon cooling in the solvent system, purification of santalin B appeared to be more complicated. While standard silica chromatography gave poor results due to aggregation to the stationary phase, sephadex size-excluding chromatography gave good results in this case.



Scheme 83 – Biomimetic cascade resulting in santalin B.

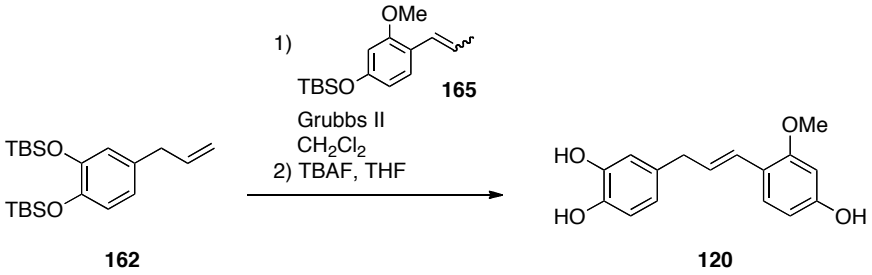
III. 1. 6. Summary

Novel allylation methods for the synthesis of benzylstyrenes have been applied, yielding coupling partners for a biomimetic approach toward the benzoxanthenone members of the santalin family. Attempts *via* Friedel-Crafts allylation, Tsuji-Trost and Heck cross-coupling failed. A π-allyl Suzuki cross-coupling with aryl boronic acid **137** was successful (Scheme 84).



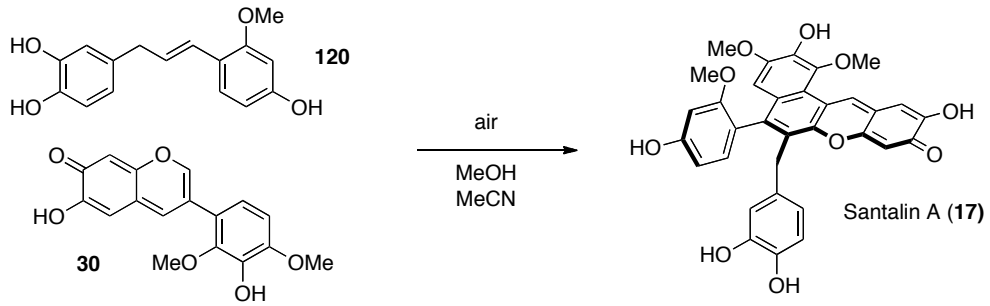
Scheme 84 – Benzylstyrene **138** suitable for santalin B could be synthesis *via* π-allyl Suzuki coupling.

The most versatile technique towards the synthesis of benzylstyrenes is olefin cross-metathesis, coupling styrenes **165** with allylphenols **162**. This very mild method has been shown to work with various substrates, even with unprotected acidic phenols (Scheme 85).



Scheme 85 – Preparation of benzylstyrene **120** suitable for santalin A *via* olefin cross-metathesis.

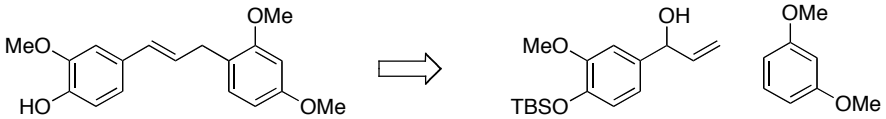
The formation of santalin A and B has been observed using mild, bioinspired conditions. During these studies it became clear that an excess of anhydrobase **30** was necessary, which arises the question whether it only plays a role as an electrophile or can act as an internal oxidant as well (Scheme 86).



Scheme 86 – Biomimetic assembly of anhydrobase **30** and benzylstyrene **120** to santalin A (**17**).

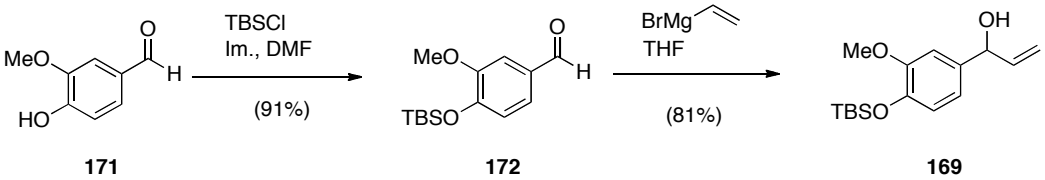
III. 2. Synthesis of Santarubin A and B

As the biomimetic cascade worked out reliably in the case of santalin A & B, the remaining members of the benzoxanthenone class, namely santarubin A & B, should be synthesized.



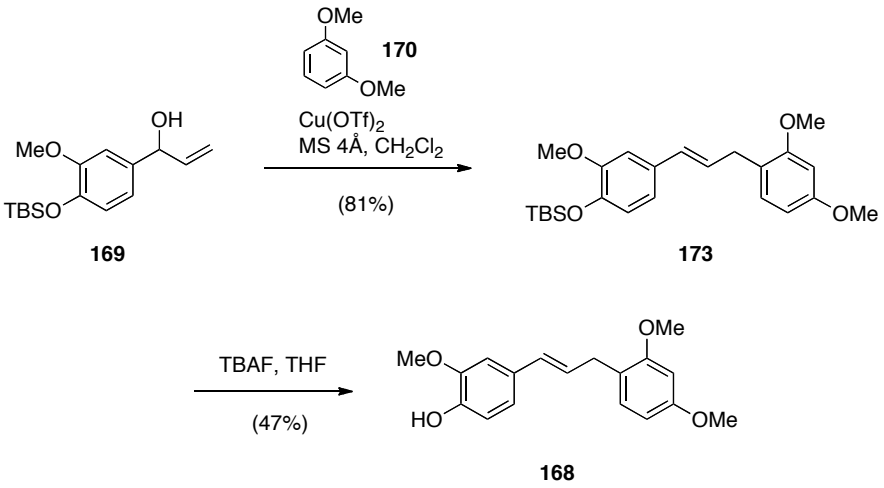
Scheme 87 – Retrosynthesis of the santarubin A benzylstyrene **168** using Friedel-Crafts allylation.

The synthesis started with the benzylstyrene coupling partner of santarubin A. From previous experience we were confident that Friedel-Crafts allylation using *O,O'*-dimethylresorcinol (**170**) with stabilized allylic cations derived from allylic alcohol **169** would result in benzylstyrene **168** (Scheme 87).[6] In order to minimize the step count Friedel-Crafts allylation was favored over olefin cross-metathesis. TBS protection of vanillin (**171**) and vinylation using vinyl Grignard afforded allylic alcohol **169** in very good overall yield (Scheme 88).



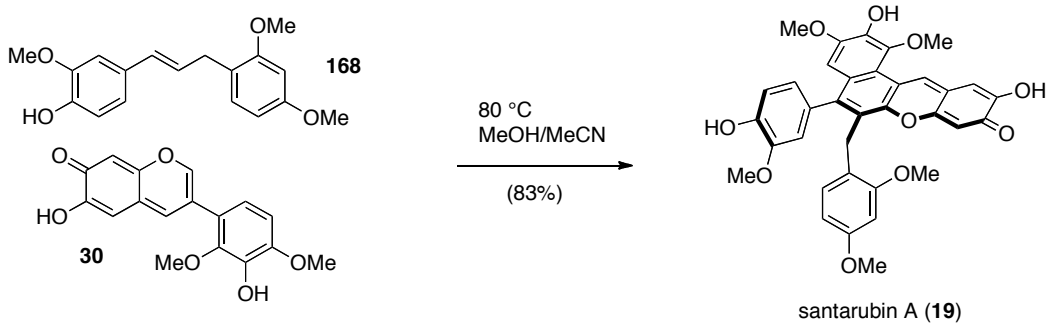
Scheme 88 – Preparation of allylic alcohol **169** from vanillin.

Treatment of allylic alcohol with catalytic amounts of copper(II) in the presence of an excess of *O,O'*-dimethylresorcinol at low temperatures gave benzylstyrene **173** in very good yield. Subsequent desilylation using standard conditions resulted in santarubin B precursor **168** (Scheme 89).



Scheme 89 – Friedel-Crafts allylation resulted in desired benzylstyrene **168**.

With the precursors in hand the reaction cascade with the previously tested conditions was attempted. Santarubin A precipitated in the reaction medium and was isolated in very good yield (Scheme 90).



Scheme 90 – Biomimetic cascade resulted in santarubin A.

The better yields might be explained by the sterical less demanding environment of the santarubin biaryl axis in comparison to santalin A and B, which is depicted in Figure 15.

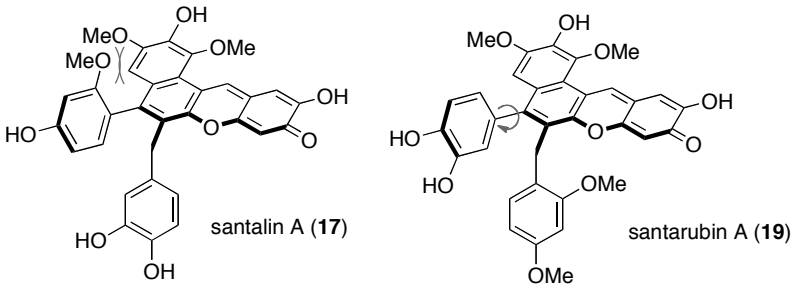
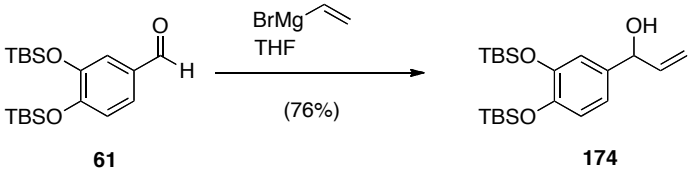


Figure 15 – Comparison of the sterical hindrance in the biaryl axis of santalin A (**17**) and santarubin A (**19**).

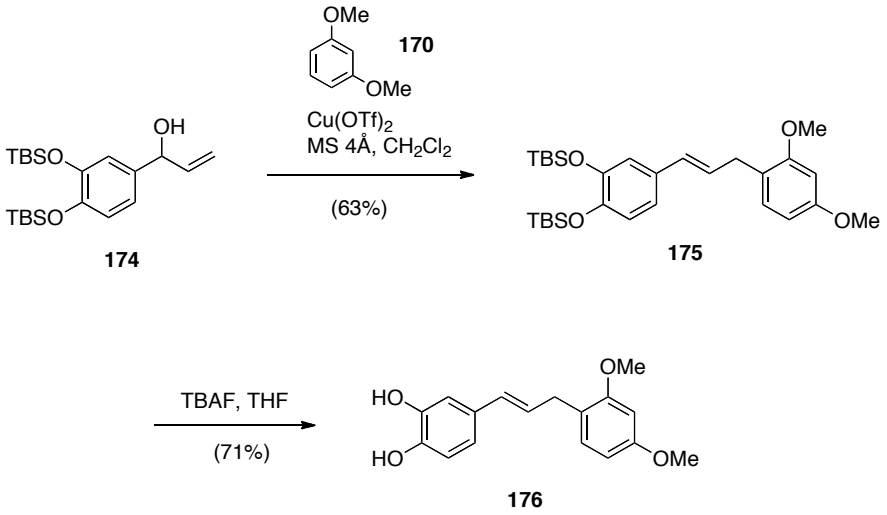
Friedel-Crafts type allylation with *O,O'*-dimethylresorcinol gave a fast entry to benzylstyrenes. Hence the same method for the synthesis of santarubin B benzylstyrene **176** was planned. Vinylation of already prepared TBS-benzaldehyde **61**, resulted in allylic alcohol **174** in good yields (Scheme 91).



61 **174**

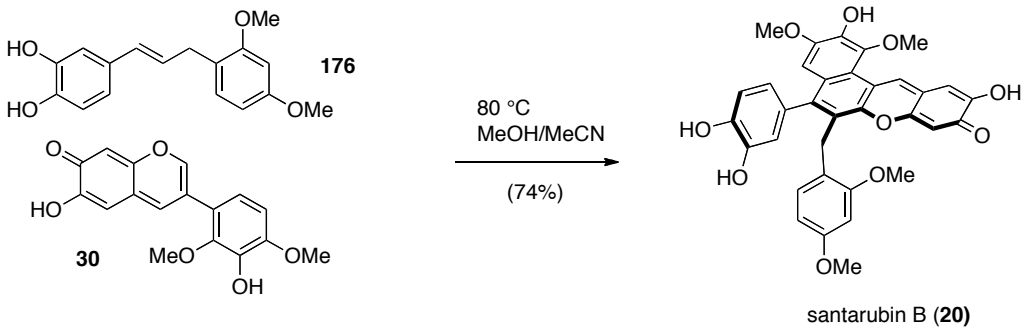
Scheme 91 – Preparation of allylic alcohol **174** using vinyl Grignard.

Allylic alcohol **174** could be transformed to benzylstyrene **175** in the same fashion, applying the same conditions as for benzylstyrene **173**. If the reaction was carried out at room temperature, double allylation of methoxy resorcinol could be observed. Desilylation resulted in benzylstyrene **176** in good yield and only four steps from commercially available starting material (Scheme 92).



Scheme 92 – Friedel-Crafts allylation resulted in desired benzylstyrene **176**.

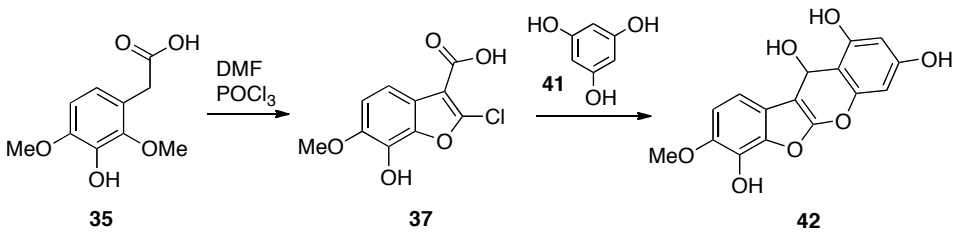
On mixing anhydrobase **30** and benzylstyrene **176** under the previously employed conditions, formation of santarubin B could be observed at elevated temperatures in very good yields (Scheme 93). The desired benzoxanthenone dye could be isolated as a precipitate from the reaction mixture.



Scheme 93 – Biomimetic cascade resulting in santarubin B.

IV. Summary, Conclusion and Future Directions

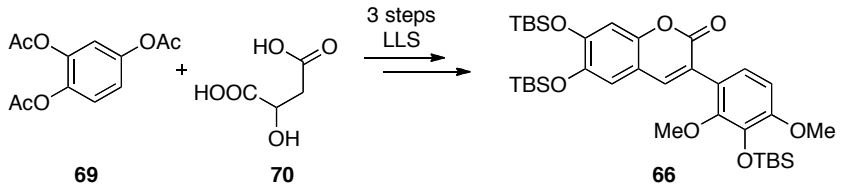
In summary, this work describes the progress towards the biomimetic synthesis of members of the santalin natural product family. Starting from classical approaches towards the anhydrobase, the presumable biosynthetic precursor, synthetic surprises lead to an approach towards the natural product ayamenin E (**40**). A formal 3+3 cycloaddition resulted in benzyl alcohol **42**, which so far could not be oxidized to ayamenin E (Scheme 94).



35 37 42

Scheme 94 – Synthesis of the reduced form of ayamenin E.

While this rapid approach failed, different attempts resulted in formation of the coumarin, including a Knoevenagel synthesis and late stage functionalizations using Suzuki and Negishi cross-couplings of protected esculetin. Use of a novel zinc base, developed by the group of P. Knochel, and a Negishi cross-coupling resulted in rapid formation of coumarin **66**, which is the common precursor for all members of the santalin family (Scheme 95).

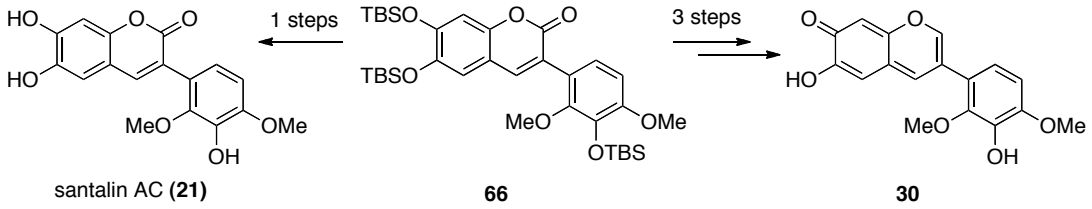


69 70 66

Scheme 95 – Rapid assembly of coumarin **66** using zinc mediated Negishi coupling.

Coumarin **66** is the branching point in the synthesis of the members of the santalin family. Deprotection of **66** lead to santalin AC (**21**), while a reduction followed by

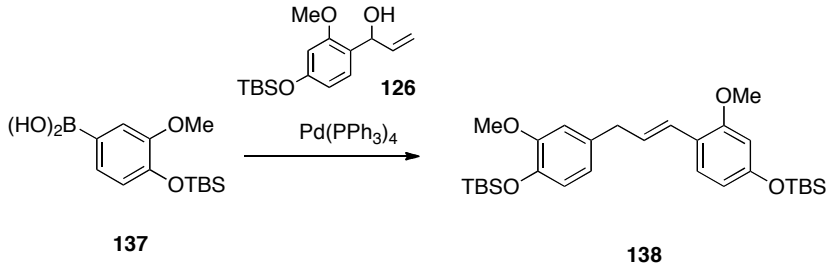
dehydration and global deprotection and deprotonation resulted in anhydrobase **30**, a vinyligous *para*-quinone methide (Scheme 96).



santalin AC **(21)** **66** **30**

Scheme 96 – Coumarin **66** acts as a branching point for santalin AC **(21)** and anhydrobase **30**.

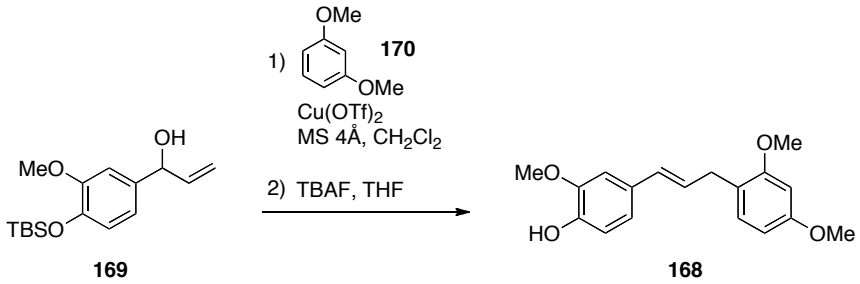
Novel allylation methods applied for the synthesis of benzylstyrenes yielded coupling partners for a biomimetic approach toward the santalin members. Successful methods include a π-allyl Suzuki cross-coupling with aryl boronic acid **137** (Scheme 97).



137 **138**

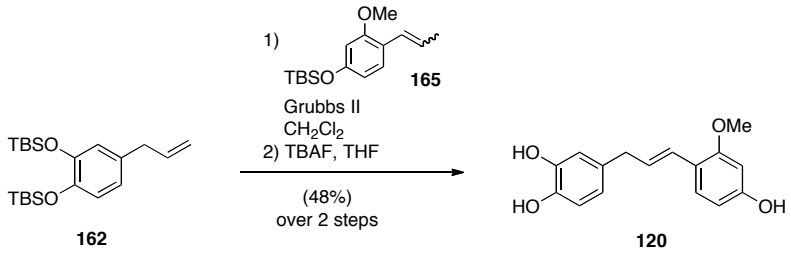
Scheme 97 – Benzylstyrene **138** suitable for santalin B could be synthesized *via* π-allyl Suzuki coupling.

Friedel-Crafts allylation of easily ionizable allylic alcohols gave a fast entry to benzylstyrenes, even though it appeared that the substitution pattern of the nucleophilic aryl ring is important (Scheme 98).



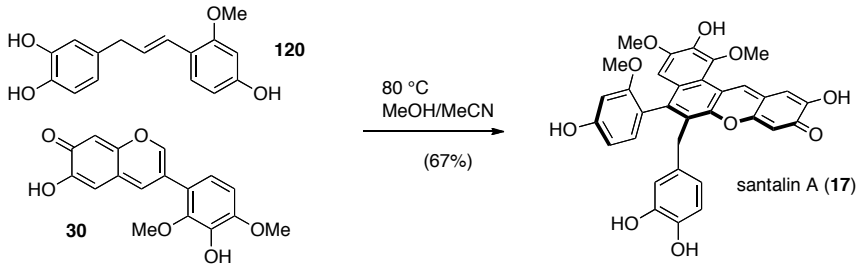
Scheme 98 – Synthesis of benzylstyrene **168** suitable for santarubin A *via* Friedel-Crafts allylation.

The most versatile technique towards the synthesis of benzylstyrenes is olefin cross-metathesis as shown in the coupling of styrene **165** with allylphenol **162**. This very mild method has been shown to work with a wide range of substrates (Scheme 99).



Scheme 99 – Preparation of benzylstyrene **120** suitable for santalin A *via* olefin cross-metathesis.

The formation of benzoxanthenone members of the santalin family has been observed using mild, bioinspired conditions. During these studies it became clear, that an excess of anhydrobase **30** was necessary, which arises the question, whether it only plays a role as an electrophile or can act as an co-oxidant as well (Scheme 100).



Scheme 100 – Biomimetic assembly of anhydrobase **30** and benzylstyrene **120** to santalin A (**17**).

With this unified method five members of the santalin family have been synthesized (Figure 16). Synthetic progress towards the synthesis of santalin Y has been accomplished by coupling benzylstyrene **120** with anhydrobase **30**. Due to the very nucleophilic nature of the pyrogallol unit, only the formation of benzoxanthenone and its reduced precursor was observed. Attempts to remove the pyrogallol unit and couple a simplified anhydrobase, revealed that an aryl ring next to the anhydrobase is necessary for shielding the electrophilic position.

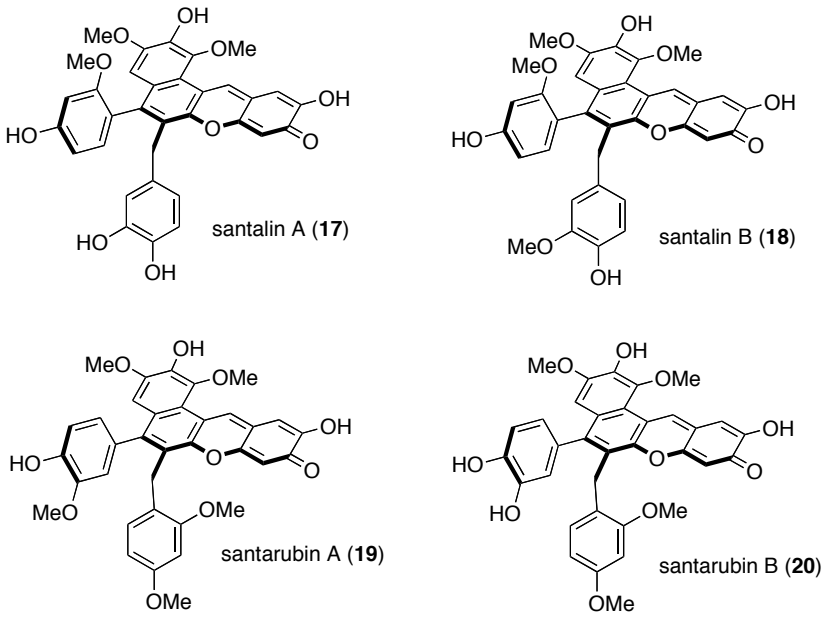
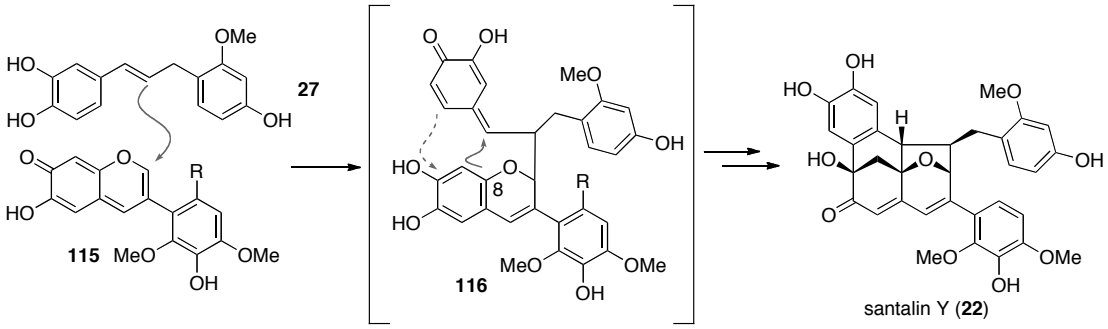


Figure 16 – Prepared members of the santalin family.

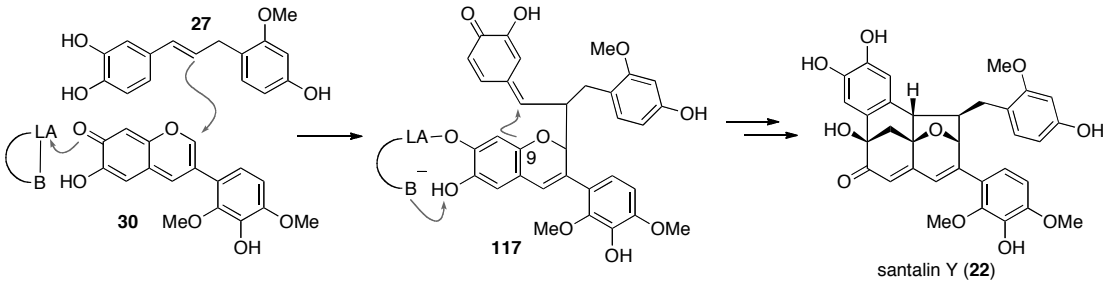
Future directions towards the synthesis of santalin Y may lead to two different approaches. The first approach includes blocking the nucleophilic pyrogallol unit by

group *R* (R = Br, TMS), thus favoring the nucleophilic attack of C8 to *para*-quinone methide. This plan could potentially lead to santalin Y (**22**) after attack *via* the dashed arrow and removing the blocking group (Scheme 101).



Scheme 101 – Future directions leading to santalin Y (R = blocking group).

A second approach involves dual catalysis, having a Lewis acidic (LA) and a Brønstedt basic site (B) incorporated in one catalyst. The Lewis acidic moiety could potentially activate anhydrobase **30** favoring the nucleophilic attack of benzylstyrene **27**. The released basic portion could then deprotonate the vicinal hydroxy group thus generating a nucleophilic position *para* to phenolate, which could attack *para*-quinone methide **117**. Subsequent Friedel-Crafts cyclization could be favored by the Lewis acid and generate santalin Y (**22**) in one step (Scheme 102).



Scheme 102 – Future directions leading to santalin Y *via* dual catalysis.

V. Experimental Details

V. 1. General Experimental Details

Unless stated otherwise, all reactions were performed in oven-dried glassware under a positive pressure of nitrogen. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone prior to use. Triethylamine was distilled over calcium hydride immediately prior to use. *n*-Butyllithium (*n*-BuLi) was titrated using iodine prior to use. All other solvents as well as starting materials and reagents were obtained from commercial sources and used without further purification or were prepared according to the cited procedures. Reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC) using E. Merck 0.25 mm silica gel 60 F254 precoated glass plates. TLC plates were visualized by exposure to ultraviolet light (UV, 254 & 365 nm) and/or exposure to an aqueous solution of ceric ammoniummolybdate (CAM) followed by heating. Flash column chromatography was performed as described by Still *et al.*[51] employing silica gel (60 Å, 40–63 µm, Merck) and a forced flow of eluant at 1.3–1.5 bar pressure. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure material.

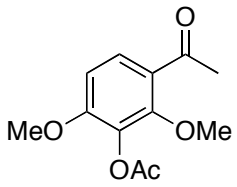
Instrumentation

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian VNMRS 300, VNMRS 400, INOVA 400 or VNMRS 600 spectrometers. Proton chemical shifts are expressed in parts per million (δ scale) and are calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: δ 7.26, d_6-DMSO: δ 2.50, d_3-MeCN: δ 1.94, d_6-acetone: δ 2.05). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad or combinations thereof. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian VNMRS 300, VNMRS 400, INOVA 400 or VNMRS 600 spectrometers. Carbon chemical shifts are expressed in parts per million (δ scale) and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.0, d_6-DMSO: δ 39.5, d_3-MeCN: δ 118.3, 29.8, d_6-acetone: δ 29.8).

Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum BX II (FTIR System). IR data are reported in frequency of absorption (cm^{-1}). Mass spectroscopy (MS) experiments were performed on a Thermo Finnigan MAT 95 (EI) or on a Thermo Finnigan LTQ FT (ESI) instrument. Melting points (mp) were determined with a Stanford Research Systems MPA120 apparatus and are uncorrected. UV-spectra (UV) were obtained using a Varian Cary 50 Scan UV/Vis spectrometer and Helma SUPRASIL precision cuvettes (10 mm light path).

V. 2. Experimental towards ayamenin E

3-acetyl-2,6-dimethoxyphenyl acetate (34)[17]



To a solution of 2,6-methoxyphenol (20.0 g, 130 mmol, 1 eq.) in Ac_2O (37.0 mL, 392 mmol, 3 eq.) was slowly added conc. H_2SO_4 (200 µL) at room temperature. The reaction mixture was heated to 140 °C for 28 h and was then allowed to cool room temperature. After addition of sat. aq. NH_4Cl (100 mL), the mixture was extracted with EtOAc (3 × 180 mL). The combined organic extracts were washed with sat. aq. NaCl (120 mL) and dried ($MgSO_4$). Flash column chromatography [Isohexane: EtOAc 8:1 → 6:1] afforded acetophenol **34** (21.9 g, 71%) as a white powder.

R_f = 0.33 (Isohexane: EtOAc 7:3).

mp (EtOAc): 107.2 – 108.5 °C.

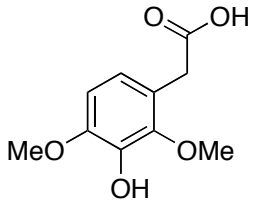
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, J = 9.0 Hz, 1H), 6.77 (d, J = 9.0 Hz, 1H), 3.87 (s, 6H), 2.60 (s, 3H), 2.37 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 168.5, 156.1, 153.5, 133.2, 128.5, 125.8, 107.3, 62.1, 56.5, 30.8, 20.7 ppm.

IR (ATR): $\tilde{\nu}$ = 2957, 1766, 1668, 1596, 1496, 1378, 1363, 866, 819 cm^{-1}.

HRMS (ESI): calcd. for $C_{12}H_{14}O_5Na^+$ $[M+Na]^+$: 261.0733,
found: 261.0734.

1-(3-hydroxy-2,4-dimethoxyphenyl)acetic acid (35)



To a stirred solution of acetophenol **34** (21.9 g, 92.1 mmol, 1 eq.) in morpholine (48.0 mL, 553 mmol, 6 eq.) were added *p*-toluenesulfonic acid (527 mg, 3.10 mmol, 3 mol-%) and S_8 (5.91 g, 184 mmol, 2 eq.). After refluxing for 2 h 30 min at 140 °C, aq. NaOH (20%, 240 mL) and tetrabutylammonium bromide (220 mg, 0.680 mmol) were added and the mixture was stirred additional 5 h 30 min at 110 °C. The reaction mixtures was diluted with HCl (conc., 90 mL) at 0 °C and extracted with EtOAc (4 × 500 mL). The combined organic phases were washed with H_2O (400 mL) and sat. aq. NaCl (400 mL) and dried ($MgSO_4$). Flash column chromatography [CH_2Cl_2: MeOH 96:4] afforded carboxylic acid **35** (8.16 g, 42 %) as a brownish solid.

R_f = 0.44 (CH_2Cl_2: MeOH 9:1).

mp (MeOH): 98.6 – 100.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (d, J = 8.5 Hz, 1H), 6.59 (d, J = 8.5 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.57 (s, 2H) ppm.

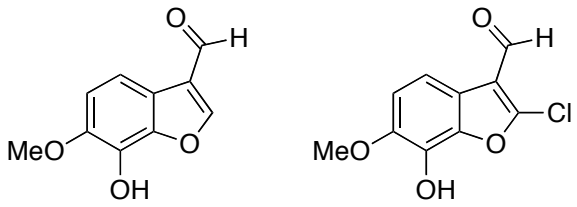
^{13}C NMR (75 MHz, $CDCl_3$): δ 220.6, 176.3, 147.7, 145.5, 138.8, 120.8, 106.6, 60.5, 56.4, 36.0 ppm.

IR (ATR): $\tilde{\nu}$ = 2981, 2941, 1695, 1498, 1339, 1219, 896, 808 cm^{-1}.

HRMS (ESI): calcd. for $C_{10}H_{11}O_5^-$ $[M–H]^-$: 211.0612,
found: 211.0614.

7-hydroxy-6-methoxybenzofuran-3-carbaldehyde (36)

2-chloro-7-hydroxy-6-methoxybenzofuran-3-carbaldehyde (37)



To $POCl_3$ (2.61 mL, 17.0 mmol, 1.8 eq.) was added DMF (2.63 mL, 34.0 mmol, 3.6 eq.) dropwise at 0 °C. After 20 min acetic acid **35** (2.00 g, 9.44 mmol, 1 eq.) was added and the resulting reaction mixture was heated up to 85 °C for 3 h. The mixture was allowed to cool to room temperature followed by the addition of ice (12 mL) and extraction with CH_2Cl_2 (3 × 200 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The residue was dissolved in EtOH (14.3 mL), aq. NaOH solution (25% w/v, 18.8 mL) and heated to 85 °C for 45 min. The solvent was removed *in vacuo* followed by addition of ice (120 mL). The solution was adjusted to pH 2 with conc. HCl. Afterwards the aqueous solution was extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with sat. aq. NaCl solution (160 mL) and dried ($MgSO_4$). Flash column chromatography [Isohexane: EtOAc 4:1] afforded chlorobenzofuran **37** (140.0 mg, 7 %) as a yellow oil and benzofuran **36** (132 mg, 7%) as a pale yellow oil.

2-chloro-7-hydroxy-6-methoxybenzofuran-3-carbaldehyde (37):

R_f: 0.48 (Isohexane:EtOAc 7:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.12 (s, 1H), 7.58 (d, J = 8.6 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 5.79 (br, 1H), 3.96 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 184.5, 151.8, 145.4, 141.6, 130.9, 119.5, 116.6, 112.0,

110.0, 57.2 ppm.

IR (ATR): $\tilde{\nu}$ = 3130 (m), 3083 (m), 3002 (w), 2873 (w), 1716 (w), 1653 (s), 1598 (m), 1562 (m), 1507 (s), 1468 (s), 1440 (s), 1349 (s), 1268 (s), 1232 (s), 1119 (s), 1077 (s), 978 (s), 782 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{10}H_6ClO_4^-$ $[M–H]^-$: 224.9960,
found: 224.9960.

7-hydroxy-6-methoxybenzofuran-3-carbaldehyde (36):

R_f: 0.33 (Isohexane: EtOAc 7:3).

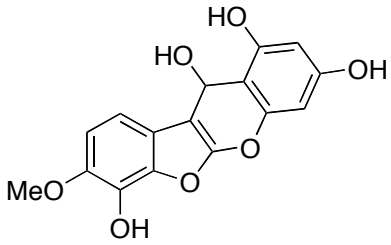
^1H NMR (300 MHz, $CDCl_3$): δ 10.13 (s, 1H), 8.21 (s, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 5.75 (br, 1H), 3.97 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 184.9, 155.7, 145.4, 144.1, 131.5, 124.0, 118.7, 112.7, 109.9, 57.3 ppm.

IR (ATR): $\tilde{\nu}$ = 3130 (m), 3083 (m), 3002 (w), 1655 (s), 1598 (m), 1562 (m), 1507 (s), 1468 (s), 1441 (s), 1350 (s), 1269 (s), 1256 (s), 1198 (m) 1120 (s), 1078 (s), 979 (s), 919 (s) 782 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{10}H_7O_4^-$ $[M–H]^-$: 191.0350,
found: 191.0350.

4'-methoxy-4H-benzofuro[2,3-*b*]chromene-3',4,5,7-tetraol (42)



To a stirred suspension of phloroglucinol (**41)** (24.5 mg, 0.19 mmol, 1.3 eq.) in Et_2O (2 mL) was added chlorobenzofuran **37** (35.0 mg, 0.15 mmol, 1 eq.) at room temperature followed by the dropwise addition of NEt_3 (8.00 µL, 580 µmol, 3.8 eq.). The resulting mixture was heated to 50 °C for 6 d. After 3 d and 5 d additional portions of phloroglucinol (5.67 mg, 0.05 mmol, 0.3 eq.; 3.78 mg, 0.03 mmol, 0.2 eq.) were added. After completion, aq. HCl solution (2.0 M, 10 mL) was added to the reaction mixture and was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and purified by flash column chromatography [CH_2Cl_2: MeOH 97:3] to afford alcohol **42** (33.0 mg, 0.10 mmol, 67%) as yellow foam.

R_f: 0.32 (CH_2Cl_2: MeOH: AcOH: H_2O 90:10:0.6:0.6).

^{1}H NMR (400 MHz, d_6-acetone): δ 8.11 (s, 1H), 6.87 (d, J = 8.7 Hz, 1H), 6.58 (d, J = 8.7 Hz, 1H), 6.41 (d, J = 2.1 Hz, 1H), 6.33 (d, J = 2.1 Hz, 1H), 5.62 (s, 1H), 3.85 (s, 3H) ppm.

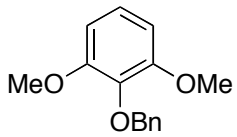
^{13}C NMR (100 MHz, d_6-acetone): δ 172.1, 162.6, 162.1, 157.2, 156.8, 144.5, 138.3, 135.3, 121.4, 120.2, 117.9, 104.3, 104.0, 99.4, 95.1, 55.5 ppm.

IR (ATR): $\tilde{\nu}$ = 3194 (br), 1607 (s), 1505 (s), 1287 (s), 1144 (s), 1079 (s), 790 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{16}H_{11}O_7^-$ $[M–H]^-$: 315.0505,
found: 315.0508.

V. 3. Experimental towards anhydrobase

2-(benzyloxy)-1,3-dimethoxybenzene (177)[52]



To a stirred solution of **33** (5.00 g, 32.4 mmol, 1 eq.) in EtOH (40 mL) were successively added K_2CO_3 (2.69 g, 19.4 mmol, 0.6 eq.), benzyl chloride (3.90 mL, 34.0 mmol, 1.05 eq.), and potassium iodide (490 mg, 3.24 mmol, 0.1 eq.) at room temperature. The reaction mixture was stirred for 12 h at this temperature. After completion, the reaction mixture was filtered through a plug of celite® and was concentrated *in vacuo*. The residual oil was washed with H_2O (120 mL) and was extracted with Et_2O (3 × 120 mL). The combined organic extracts were washed with H_2O (100 mL), sat. aq. NaCl (100 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 20:1] to afford **177** (4.49 g, 57 %) as a pale yellow oil.

R_f: 0.95 (Isohexane:EtOAc 7:3).

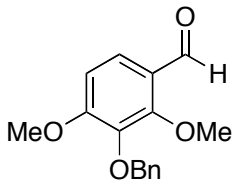
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 – 7.48 (m, 2H), 7.39 – 7.27 (m, 3H), 7.00 (t, J = 8.3 Hz, 1H), 6.58 (d, J = 8.3 Hz, 2H), 5.02 (s, 2H), 3.83 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 138.2, 137.4, 128.7, 128.3, 128.0, 123.9, 105.6, 75.2, 56.3 ppm.

IR (ATR): $\tilde{\nu}$ = 3062 (w), 3001 (w), 2937 (w), 2835 (w), 1594 (m), 1492 (m), 1475 (s), 1434 (m), 1294 (s), 1252 (s), 1216 (s), 1105 (s), 1089 (s), 985 (m), 772 (m), 728 (s), 694 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{15}H_{16}O_3^+$ $[M^\bullet]^+$: 244.1094,
found: 244.1091

3-(benzyloxy)-2,4-dimethoxybenzaldehyde (45)[53]



To a stirred mixture of benzyl ether **177** (4.49 g, 18.4 mmol, 1 eq.) in DMF (3.00 mL, 39.0 mmol, 2.1 eq.) was added $POCl_3$ (4.30 mL, 46.0 mmol, 2.5 eq.) at 2 °C over the period of 1 h 30 min. After complete addition, the reaction mixture was stirred for additional 1 h at room temperature and was then heated to 70 °C for 3 h. After completion, the reaction mixture was cooled to room temperature and poured into ice water (40 mL). The biphasic mixture was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were washed with sat. aq. $NaHCO_3$ (2 × 50 mL), H_2O (50 mL), sat. aq. NaCl (50 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography [Isohexane:EtOAc 10:1] to afford benzaldehyde **45** (2.75 g, 55 %) as a yellow oil.

R_f: 0.22 (Isohexane:EtOAc 7:1).

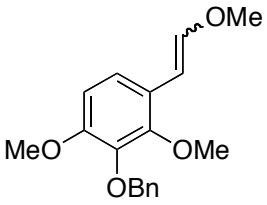
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.25 (d, J = 0.8 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.42 – 7.30 (m, 3H), 6.76 (d, J = 8.8 Hz, 1H), 5.04 (s, 2H), 4.02 (s, 3H), 3.91 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 189.1, 159.7, 157.6, 140.7, 137.4, 128.6, 128.6, 128.4, 124.7, 123.7, 107.7, 75.6, 62.8, 56.4 ppm.

IR (ATR): $\tilde{\nu}$ = 3337 (w), 3063 (w), 2942 (w), 2840 (w), 1676 (s), 1586 (s), 1493 (s), 1461 (s), 1384 (m), 1285 (s), 1257 (s), 1219 (m), 1089 (s), 1000 (s), 911 (m), 735 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{16}H_{16}O_4^+$ $[M^\bullet]^+$: 272.1043,
found: 272.1045.

2-(benzyloxy)-1,3-dimethoxy-4-(2-methoxyvinyl)benzene (47)



To a stirred suspension of methoxymethyl triphenylphosphonium chloride (864 mg, 2.52 mmol, 2 eq.) in THF (3 mL) at 0 °C was added a mixture of KO*t*-Bu (283 mg, 2.52 mmol, 2 eq.) in THF (2 mL) dropwise over a period of 10 min. The solution was stirred for 30 min at room temperature and after this time **45** (343 mg, 1.26 mmol, 1 eq.) in THF (1.5 mL) was added at 0 °C dropwise over a period of 5 min. The reaction mixture was stirred for 10 h at room temperature. After completion, the reaction mixture was poured into H_2O (20 mL) and was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with sat. aq. NaCl (20 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography [Isohexane:EtOAc 10:1] to afford methyl enol ether **47** (349 mg, 92 %) as a pale yellow oil.

Enol ether **47** was obtained as a mixture of diastereomers 1.5:1 (*E*:*Z)*.

R_f: 0.59 (Isohexane:EtOAc 7:3).

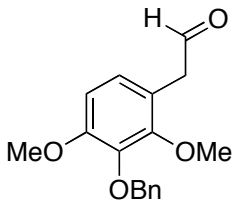
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.8 Hz, 1H), 7.54 – 7.48 (m, 4H), 7.43 – 7.27 (m, 6H), 7.04 (d, J = 13.0 Hz, 1H), 6.97 (dd, J = 8.7, 0.5 Hz, 1H), 6.65 (dd, J = 16.3, 8.7 Hz, 2H), 6.14 (d, J = 7.2 Hz, 1H), 5.95 (d, J = 13.0 Hz, 1H), 5.53 (d, J = 7.2 Hz, 1H), 5.02 (s, 2H), 5.01 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.69 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 152.2, 151.0, 148.8, 147.4, 141.9, 141.6, 138.2, 138.1, 128.5, 128.5, 128.5, 128.4, 128.1, 128.0, 124.6, 123.45, 123.0, 120.3, 108.2, 107.7, 100.1, 98.8, 75.5, 75.4, 61.5, 61.0, 60.8, 56.6, 56.3, 56.3 ppm.

IR (ATR): $\tilde{\nu}$ = 3413 (br), 2935 (w), 2834 (w), 1648 (m), 1595 (m), 1491 (s), 1456 (s), 1417 (s), 1372 (m), 1274 (s), 1261 (s), 1220 (s), 1153 (m), 1090 (s), 1009 (s), 809 (m), 735 (s), 695 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{18}H_{20}O_4^+$ $[M^{\bullet}]^+$: 300.1356,
found: 300.1348.

2-(3-(benzyloxy)-2,4-dimethoxyphenyl)acetaldehyde (44)



To a stirred solution of enol ether **47** (100 mg, 333 µmol, 1 eq.) in acetone (3 mL) was added aq. HCl (6 M, 0.300 mL, 1.80 mmol, 30 eq.) at room temperature. The reaction mixture was stirred for 2 h 30 min at room temperature. After completion, the reaction mixture was added to sat. aq. NH_4Cl (10 mL) and was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with sat. aq. NaCl (10 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 8:1] to afford aldehyde **44** (67.0 mg, 70 %) as a pale yellow oil.

R_f: 0.55 (Isohexane:EtOAc 7:3).

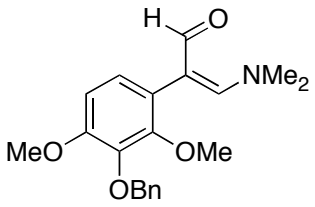
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.69 (t, J = 2.1 Hz, 1H), 7.51 – 7.47 (m, 2H), 7.41 – 7.30 (m, 3H), 6.85 (d, J = 8.5 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 5.03 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.61 (d, J = 2.1 Hz, 2H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 154.0, 152.7, 141.4, 137.7, 128.5, 128.5, 128.2, 125.6, 118.7, 107.7, 75.3, 61.2, 56.3, 45.3 ppm.

IR (ATR): $\tilde{\nu}$ = 3402 (br), 2972 (w), 2937 (w), 1678 (w), 1602 (w), 1494 (s), 1462 (s), 1374 (m), 1277 (s), 1258 (m), 1195 (m), 1094 (s), 1041 (s), 1011 (s), 798 (s), 737 (s), 695 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{17}H_{18}O_4^+$ $[M^{\bullet}]^+$: 286.1200,
found: 286.1196.

(*Z*)-2-(3-(benzyloxy)-2,4-dimethoxyphenyl)-3-(dimethylamino)acrylaldehyde (49)



To a stirred solution of acetaldehyde **44** (67.0 mg, 234 µmol, 1 eq.) in DMF (2 mL) was added DMF dimethyl acetal (50.0 µL, 376 µmol, 1.6 eq.) at room temperature in one portion. The reaction mixture was stirred at this temperature for 12 h. After completion, the reaction mixture was poured in H_2O (15 mL) and was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with sat. aq. NaCl (10 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [CH_2Cl_2:MeOH 19:1] to afford **49** (67.0 mg, 85 %) as colorless needles.

R_f: 0.57 (CH_2Cl_2:MeOH 10:1).

mp (MeOH): 64.9 – 67.2 °C.

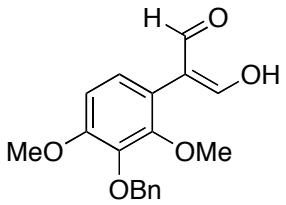
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.09 (s, 1H), 7.53 – 7.42 (m, 2H), 7.39 – 7.26 (m, 3H), 6.81 (bs, 1H), 6.81 (d, J = 8.5 Hz, 1H), 6.67 (d, J = 8.5 Hz, 1H), 5.11 (d, J = 11.0 Hz, 1H), 4.99 (d, J = 11.0 Hz, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 2.78 (br s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.1, 189.8, 159.2, 153.6, 152.8, 141.2, 138.0, 128.5, 128.4, 128.0, 127.5, 121.2, 111.4, 107.6, 75.0, 61.1, 56.1 ppm.

IR (ATR): $\tilde{\nu}$ = 2932 (w), 1582 (s), 1496 (m), 1454 (m), 1396 (s), 1272 (s), 1231 (m), 1194 (m), 1174 (m) 1091 (s), 994 (m), 790 (m), 750 (s), 696 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{20}H_{24}O_4N^+$ $[M+H]^+$: 342.1700,
found: 342.1704.

(*Z*)-2-(3-(benzyloxy)-2,4-dimethoxyphenyl)-3-hydroxyacrylaldehyde (43)



To a stirred solution of **49** (100 mg, 400 µmol, 1 eq.) in EtOH (10 mL) was added aq. NaOH (1 M, 2.40 mL, 2.40 mmol, 6 eq.) at room temperature. The reaction mixture was heated to 70 °C for 6 h. After completion, sat. aq. NH_4Cl (10 mL) was added and the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with sat. aq. NaCl (10 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [CH_2Cl_2:MeOH 19:1] to afford **43** (74.0 mg, 83 %) as a colorless oil.

R_f: 0.43 (CH_2Cl_2:MeOH 10:1).

^{1}H NMR (400 MHz, d_6-acetone): δ 8.54 (s, 2H), 7.56 – 7.51 (m, 2H), 7.41 – 7.32 (m, 3H), 6.88 (d, J = 8.5 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 5.02 (s, 2H), 3.88 (s, 3H), 3.76 (s, 3H) ppm.

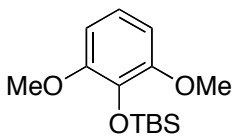
^{13}C NMR (100 MHz, d_6-acetone): δ 184.0 (*), 155.3, 153.2 (**), 143.0, 139.8, 129.6, 129.4, 129.1, 126.6 (*), 118.5 (**), 108.8 (*), 109.3, 76.0, 61.8, 57.0 ppm.

IR (ATR): $\tilde{\nu}$ = 2923 (s), 2852 (s), 1584 (s), 1495 (m), 1414 (s), 1283 (m), 1093 (s), 1013 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{18}H_{17}O_5^-$ $[M–H]^-$: 313.1081,
found: 313.1075.

(*) obscured carbon was detected by HSQC.
(**) obscured carbon was detected by HMBC.

***tert*-butyl(2,6-dimethoxyphenoxy)dimethylsilane (178)**



To a stirred solution of 2,6-dimethoxyphenol (**33**) (3.00 g, 19.5 mmol, 1 eq.) in DMF (20 mL) at 0 °C was added imidazole (1.46 g, 20.5 mmol, 2.2 eq.), 4-dimethylaminopyridine (240 mg, 1.95 mmol, 0.1 eq.) and TBSCl (3.09 g, 1.05 mmol, 1.1 eq.). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the mixture was diluted with H_2O (15 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with sat.

aq. NaCl solution (20 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography [Isohexane: EtOAc 10:1] to provide **178** (5.05 g, 18.8 mmol, 97%) as colorless needles.

R_f: 0.56 (Isohexane:EtOAc 10:1).

mp (EtOAc): 42.9 – 43.7 °C.

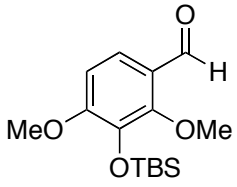
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86 (t, J = 8.3 Hz, 1H), 6.57 (d, J = 8.3 Hz, 2H), 3.82 (s, 6H), 1.04 (s, 9H), 0.16 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 151.9, 134.5, 120.6, 105.4, 55.8, 25.8, 18.7, –4.6 ppm.

IR (ATR): $\tilde{\nu}$ = 2996 (w), 2952 (m), 2930 (m), 2896 (m), 2857 (m), 2837 (m), 1594 (m), 1503 (m), 1476 (m), 1445 (m), 1436 (m), 1390 (w), 1361 (w), 1302 (m), 1246 (s), 1186 (w), 1171 (s), 1041 (w), 910 (m), 837 (m), 824 (m), 809 (m), 780 (m), 768 (m), 741 (m), 718 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{14}H_{24}O_3Si^-$ $[M–H]^-$: 268.1495,
found: 268.1487.

3-((*tert*-butyldimethylsilyl)oxy)2,4-dimethoxybenzaldehyde (55)



To a stirred solution of TMEDA (7.80 mL, 52.2 mmol, 1.4 eq.) in hexane (45 mL)

was added *n*-BuLi (2.5 M solution in hexane; 16.4 mL, 41.0 mmol, 1.1 eq.) and stirred for 30 min at 0 °C. A solution of **178** (10.0 g, 37.3 mmol, 1 eq.) in hexane (12 mL) was added to the mixture over a period of 1 h at –14 °C. After keeping the mixture at –14 °C for 1 h the reaction was allowed to warm to room temperature and stirred for additional 22 h. DMF (4.80 mL, 63.4 mmol, 1.7 eq.) was added slowly to the reaction mixture and the solution was maintained at 0 °C for 1 h 30 min. After addition of sat. aq. NH_4Cl (30 mL) it was stirred 10 h at room temperature and the resulting mixture was diluted with H_2O (100 mL) and extracted with Et_2O (4 × 150 mL) The combined organic extracts were washed with sat. aq. NaCl (150 mL) and dried ($MgSO_4$). Flash column chromatography [Isohexane: EtOAc 30:1] afforded **55** (4.90 g, 50%) as a pale yellow solid.

R_f = 0.61 (Isohexane:EtOAc 1:4).

mp (EtOAc) = 29.7 – 30.2 °C.

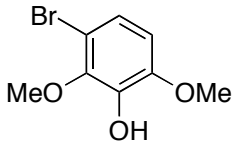
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.22 (d, J = 0.5 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 6.73 (dd, J = 8.7, 0.5 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 1.03 (s, 9H), 0.16 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 189.2, 157.5, 155.2, 138.2, 123.7, 121.8, 107.3, 62.1, 55.5, 25.7, 18.6, –4.7 ppm.

IR (ATR): $\tilde{\nu}$ = 2934, 2859, 1680, 1583, 1385, 1361, 831, 816 cm^{-1}.

HRMS (ESI): calcd. for $C_{15}H_{31}O_4Si^-$ $[M–H]^-$: 195.1366,
found: 195.1402.

3-bromo-2,6-dimethoxyphenol (57)[26]



To a stirred solution of 2,6-dimethoxyphenol (**33**) (6.00 g, 38.9 mmol, 1 eq.) in CCl_4 (100 mL) was added bromine (6.20 mL, 38.9 mmol, 1 eq.) in CCl_4 (40 mL) dropwise at –10 °C. After 5 min of stirring at this temperature, the reaction mixture was diluted with CCl_4 (100 mL) and washed with H_2O (3 × 200 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) the combined organic extracts were washed with sat. aq. NaCl solution (100 mL) and dried ($MgSO_4$). Concentration *in vacuo* afforded bromide **57** (8.12 g, 98%) as a pale brown oil, which was directly used in the next step.

R_f: 0.51 (Isohexane:EtOAc 7:3).

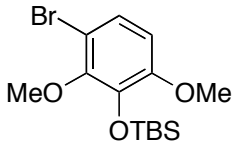
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.03 (d, J = 8.9 Hz, 1H), 6.58 (d, J = 8.9 Hz, 1H), 5.65 (br, 1H, *O*H), 3.94 (s, 3H), 3.90 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 147.3, 144.4, 139.9, 122.4, 108.4, 107.8, 60.7, 56.4 ppm.

IR (ATR): $\tilde{\nu}$ = 3493 (m), 3432 (m), 3094 (w), 3005 (w), 2940 (m), 2838 (m), 1601 (m), 1488 (s), 1468 (s), 1441 (m), 1331 (m), 1291 (m), 1215 (s), 1085 (s), 908 (w), 876 (m), 786 (m), 700 (w), 642 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_8H_8BrO_3^-$ $[M–H]^-$: 230.9662,
found: 230.9665.

(3-bromo-2,6-dimethoxyphenoxy)(*tert*-butyl)dimethylsilane (75)



To a stirred solution of phenol **57** (7.50 g, 32.3 mmol, 1 eq.) in DMF (40 mL) was added successively TBSCl (7.28 g, 48.5 mmol, 1.5 eq.), imidazole (6.58 g, 96.6 mmol, 3.0 eq.) and 4-dimethylaminopyridine (590 mg, 4.83 mmol, 0.15 eq.) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 45 min. After completion, the reaction mixture was diluted with H_2O (70 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with aq. NaCl solution (10%, 2 × 150 mL), sat. aq. NaCl solution (70 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography [Isohexane:EtOAc 30:1] to provide **75** (6.78 g, 90%) as a colorless oil.

R_f: 0.60 (Isohexane:EtOAc 30:1).

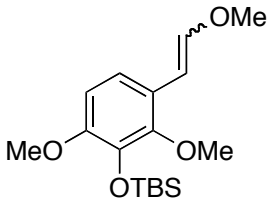
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, J = 8.9 Hz, 1H), 6.57 (d, J = 8.9 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 1.04 (s, 9H), 0.18 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 151.8, 149.3, 139.8, 124.0, 108.7, 108.3, 60.2, 55.5, 25.7, 18.6, –4.8 ppm.

IR (ATR): $\tilde{\nu}$ = 3085 (w), 2998 (m), 2954 (m), 2933 (s), 2896 (m), 2857 (s), 1574 (m), 1479 (s), 1462 (s), 1441 (m), 1418 (m), 1301 (m), 1249 (m), 1219 (s), 1092 (s), 1015 (m), 935 (s), 918 (m), 827 (m), 814 (m), 782 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{13}H_{20}BrO_3Si^-$ $[M–CH_3]^-$: 331.0371,
found: 331.0368.

***tert*-butyl(2,6-dimethoxy-3-(2-methoxyvinyl)phenoxy)dimethylsilane (57)**



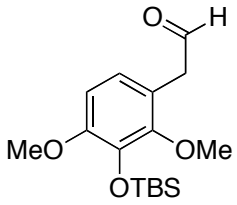
To a stirred solution of methoxymethyl triphenylphosphonium chloride (4.63 g, 13.5 mmol, 2 eq.) in THF (20 mL), a solution of KO*t*Bu (1.52 g, 13.5 mmol, 2 eq.) in THF (20 mL) was added at 0 °C. This mixture was stirred for 30 min at 0 °C, and a solution of benzaldehyde **55** (2.00 g, 6.75 mmol, 1 eq.) in THF (20 mL) was added during 30 min at room temperature. After stirring for additional 21 h at room temperature, the mixture was diluted with sat. aq. NH_4Cl (70 mL) and extracted with EtOAc (4 × 100 mL). The combined organic extracts were washed with sat. aq. NaCl (100 mL) and dried ($MgSO_4$). Flash column chromatography [Isohexane: EtOAc 30:1] afforded **57** (2.10 g, 96%) as a colorless oil.

R_f = 0.32 (Isohexane: EtOAc 30:1).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60 (d, J = 8.9 Hz, 1H), 7.01 (d, J = 13.0 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.58 (t, J = 8.9 Hz, 2H), 6.10 (d, J = 7.2 Hz, 1H), 5.93 (d, J = 13.1 Hz, 1H), 5.50 (d, J = 7.2 Hz, 1H), 3.79 – 3.64 (m, 18H), 1.01 (s, 9H), 1.01 (s, 9H), 0.13 (s, 6H), 0.13 (s, 6H) ppm.

This compound was obtained as a mixture of diastereomers (E:Z) 1.7:1 and was directly used in the next step without further purification and characterization.

2-(3-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethoxyphenyl)acetaldehyde (58)



To a stirred solution of enol ether **57** (2.10 g, 6.50 mmol, 1 eq.) in acetone (65 mL) was added slowly aq. HCl (6 M; 6.50 mL, 38.4 mmol, 9.1 eq.). After stirring for 70 min at room temperature, the reaction mixture was diluted with sat. aq. $NaHCO_3$ (90 mL) and extracted with EtOAc (3 × 110 mL). The combined organic extracts were washed with sat. aq. NaCl and dried ($MgSO_4$). Flash column chromatography [Isohexane: EtOAc 20:1] afforded **58** (1.19 g, 59%) as a colorless oil.

R_f = 0.38 (Isohexane: EtOAc 16:1).

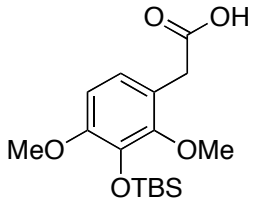
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.68 (t, J = 2.3 Hz, 1H), 6.71 (d, J = 8.6 Hz, 1H), 6.62 (d, J = 8.6 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.59 (d, J = 2.3 Hz, 2H), 1.02 (s, 9H), 0.15 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 200.1, 151.8, 150.7, 138.7, 122.4, 118.6, 107.3, 60.1, 55.4, 45.0, 25.8, 18.6, 4.6 ppm.

IR (ATR): $\tilde{\nu}$ = 2858, 2837, 2716, 1726, 1600, 1465, 1099, 835 cm^{-1}.

HRMS (ESI): calcd. for $C_{16}H_{35}O_4Si^+$ $[M+H]^+$: 311.1679,
found: 311.1677.

2-(3-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethoxyphenyl)acetic acid (59)



To a stirred solution of arylacetaldehyde **58** (1.19 g, 3.82 mmol, 1 eq.), NaH_2PO_4 (1.04 g, 11.5 mmol, 3 eq.) and 2-methyl-2-butene (3.25 mL, 30.6 mmol, 7.9 eq.) in *t*-BuOH/water (3:1, 50 mL) was added sodium chlorite (1.04 g, 11.5 mmol, 3 eq.). After stirring for 30 min at room temperature, the reaction mixture was diluted with sat. aq. NH_4Cl (50 mL) and extracted with EtOAc (3 × 70 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography [Isohexane: EtOAc 3:1] afforded acid **59** (0.990 g, 79%) as a white solid.

R_f = 0.11 (Isohexane: EtOAc 10:1).

mp (EtOAc) = 81.3 – 82.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.61 (s, 2H), 1.01 (s, 9H), 0.15 (s, 6H) ppm.

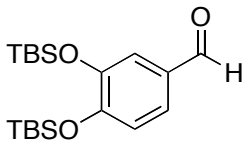
^{13}C NMR (75 MHz, $CDCl_3$): δ 176.2(*), 151.7, 150.2, 138.5, 122.1, 119.9, 107.1, 60.2, 55.3, 35.5, 25.8, 18.6, –4.6 ppm.

(*) obscured C detected by HMBC

IR (ATR): $\tilde{\nu}$ = 2930, 2858, 1717, 1499, 1466, 1095, 1010, 838 cm^{-1}.

HRMS (ESI): calcd. for $C_{16}H_{25}O_5Si^-$ $[M–H]^-$: 325.1471,
found: 325.1477.

3,4-bis(*tert*-butyldimethylsilyloxy)benzaldehyde (61)[54]



To a stirred solution of benzaldehyde **60** (5.03 g, 36.4 mmol, 1 eq.) in DMF (20 mL) was added TBSCl (16.5 g, 109 mmol, 3 eq.) imidazole (14.9 g, 218 mmol, 6 eq.), 4-dimethylaminopyridine (1.33 g, 10.9 mmol, 0.3 eq.) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 7 h. After completion, H_2O (100 mL) was added to the reaction mixture and was extracted with Et_2O (3 × 130 mL). The combined organic extracts were washed with aq. NaCl (10%, 2 × 70 mL), sat. aq. NaCl (70 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography [Isohexane:EtOAc 30:1] to afford TBS-benzaldehyde **61** (11.1 g, 83%) as yellow needles.

R_f: 0.49 (Isohexane:EtOAc 10:1).

mp (EtOAc): 45.3 – 47.1 °C.

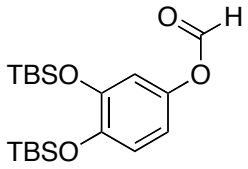
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.39 – 7.34 (m, 2H), 6.96 – 6.92 (m, 1H), 1.00 (s, 9H), 1.00 (s, 9H), 0.25 (s, 6H), 0.23 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 191.0, 153.5, 147.8, 130.9, 125.4, 121.0, 120.7, 26.0, 26.0, 18.7, 18.6, –3.9, –4.0 ppm.

IR (ATR): $\tilde{\nu}$ = 2952 (m), 2928 (m), 2856 (m), 1694 (s), 1592 (s), 1506 (s), 1284 (s), 1251 (s), 1151 (s), 896 (s), 802 (s), 778 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{19}H_{35}O_3Si_2^+$ $[M+H]^+$: 367.2119,
found: 367.2119.

3,4-*bis*((*tert*-butyldimethylsilyl)oxy)phenyl formate (62)



To a stirred solution of benzaldehyde **61** (500 mg, 1.36 mmol, 1 eq.) in CH_2Cl_2 (10 mL) was added *m*CPBA (352 mg, 2.04 mmol 1.5 eq.). The reaction mixture was refluxed for 6 h 20 min at 60 °C, then diluted with aq. $NaHCO_3$ (5 % w/v, 10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. **62** was obtained as yellow oil (0.532 g, 98%) and used for the next reaction without purification.

R_f = 0.28 (Isohexane: EtOAc 30:1).

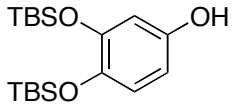
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.79 (s, 1H), 8.23 (s, 1H), 6.78 (d, J = 8.6 Hz, 1H), 6.57 (d, J = 8.6 Hz, 1H), 0.99 – 0.94 (m, 18H), 0.20 – 0.16 (m, 12H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 147.4, 145.3, 143.6, 120.8, 114.1, 113.4, 25.9, 25.9, 18.4 (2C), –4.1, –4.2 ppm.

IR (ATR): $\tilde{\nu}$ = 2930, 2859, 1691, 1574, 1473, 1094, 897, 837 cm^{-1}.

HRMS (ESI): calcd. for $C_{19}H_{33}O_4Si_2^-$ $[M–H]^-$: 381.1917,
found: 381.1923.

3,4-bis((*tert*-butyldimethylsilyl)oxy)phenol (64)



To benzaldehyde **61** (499 mg, 1.36 mmol, 1 eq.) in CH_2Cl_2 (10 mL) was added *m*CPBA (0.352 mg, 2.04 mmol, 1.5 eq.). The reaction mixture was stirred at 60 °C for 5 h. To the reaction mixture was added aq. $NaHCO_3$ (5% w/v; 10 mL) and was extracted with EtOAc (3 × 15 mL). The organic phases were concentrated *in vacuo* and a mixture of aq. KOH (5%w/v)/MeOH (4:1, 15 mL) was added and stirred at room temperature for 1 h 40 min. The reaction mixture was acidified with aq. HCl (2 M, 4 mL) and was extracted with EtOAc (3 × 15 mL). The organic phases were washed with sat. aq. $NaHCO_3$ (15 mL), sat. aq. NaCl (15 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography [Isohexane:EtOAc 20:1] to afford phenol **64** (428 mg, 89%) as a white wax.

R_f = 0.27 (Isohexane: EtOAc 4:1).

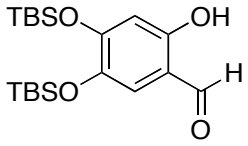
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (d, J = 8.6 Hz, 1H), 6.37 (d, J = 3.0 Hz, 1H), 6.28 (dd, J = 8.6, 3.0 Hz, 1H), 4.32 (s, 1H, *O*H), 0.98 (s, 9H), 0.97 (s, 9H), 0.20 (s, 6H), 0.16 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 149.9, 147.6, 141.2, 121.4, 109.0, 107.8, 26.2, 26.2, 18.7, 18.6, –3.9, –3.9 ppm.

IR (ATR): $\tilde{\nu}$ = 3185 (br), 2928 (s), 2885 (m), 2857 (s), 1600 (w), 1510 (s), 1453 (s), 1361 (w), 1312 (w), 1253 (s), 1226 (s), 1174 (s), 1112 (m), 989 (s), 926 (w), 902 (s), 838 (s), 776 (s), 695 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{18}H_{33}O_3Si_2^-$ $[M–H]^-$: 353.1974,
found: 353.1967.

4,5-bis((*tert*-butyldimethylsilyl)oxy)-2-hydroxybenzaldehyde (63)



a) Fries rearrangement

To a stirred solution of formylester **62** (100 mg, 0.261 mmol, 1 eq.) in CH_2Cl_2 (3 mL) was added BCl_3 (0.316 mL, 1 M in CH_2Cl_2, 1.2 eq.) at –12 °C. The reaction mixture was maintained at –10 °C for 30 min, then warmed up to 0 °C during 1 h. The mixture was stirred 2 h at 0 °C, 2 h at room temperature, 1 h at 30 °C and 1 h at 40 °C. After the mixture was stirred at 50 °C for 2 h CH_2Cl_2 was evaporated and replaced by dichloroethane. After 24 h at 60 °C, the mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with sat. aq. NaCl (12 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (Isohexane: EtOAc 10:1) afforded **63** (26 mg, 26%) as a white solid.

b) Directed ortho-formylation

To a stirred solution of phenol **64** (3.41 g, 9.61 mmol, 1 eq.) in THF (96 mL) was added $MgCl_2$ (1.83 g, 19.2 mmol, 2.0 eq.), NEt_3 (2.67 mL, 19.2 mmol, 2.0 eq.) and paraformaldehyde (866 mg, 28.8 mmol, 3.0 eq.). The reaction mixture was stirred at 60 °C for 4 h. After completion, sat. aq. NH_4Cl (50 mL) was added to the reaction mixture and was extracted with EtOAc (3 × 100 mL), washed with sat. aq. NaCl (6 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography [Isohexane:EtOAc 20:1] to afford **63** (3.18 g, 86%) as a white solid.

R_f: 0.71 (Isohexane: EtOAc 4:1).

mp (EtOAc) = 72.8 – 73.8 °C.

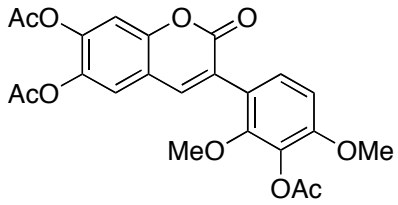
^{1}H NMR (300 MHz, $CDCl_3$): δ 11.02 (s, 1H, *O*H), 9.61 (s, 1H), 6.88 (s, 1H), 6.39 (s, 1H), 1.00 – 0.94 (m, 18H), 0.28 – 0.15 (m, 12H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 194.1, 158.2, 156.3, 140.6, 123.3, 114.5, 108.4, 25.9, 25.8, 18.6, 18.4, –4.0, –4.2 ppm.

IR (ATR): $\tilde{\nu}$ = 2930, 2897, 2858, 1651, 1497, 1350, 885, 861 cm^{-1}.

HRMS (ESI): calcd. for $C_{19}H_{33}O_4Si_2^-$ $[M–H]^-$: 381.1917,
found: 381.1920

3-(3-acetoxy-2,4-dimethoxyphenyl)-2-oxo-2*H*-chromene-6,7-diyl diacetate (65)



To a stirred solution of acid **59** (100 mg, 306 µmol, 1 eq.) and benzaldehyde **63** (117 mg, 306 µmol, 1 eq.) in acetic anhydride (0.5 mL) was added potassium acetate (54.0 mg, 551 µmol, 1.8 eq.). The reaction mixture was heated to 135 °C for 1 h. After completion, reaction mixture was cooled to room temperature, added to sat. aq. $NaHCO_3$ (10 mL) and was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with sat. aq. NaCl (10 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 3:2] to afford acetoxy-santalin AC **65** (33.0 mg, 24 %) as a pale yellow solid.

R_f: 0.60 (CH_2Cl_2:MeOH 99:1).

mp (EtOAc): 85.3 – 89.7 °C.

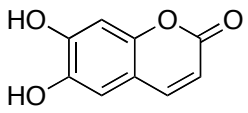
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.33 (s, 1H), 7.30 (d, J = 8.7 Hz, 1H), 7.24 (s, 1H), 6.79 (d, J = 8.7 Hz, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 2.37 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 168.7, 168.4, 167.8, 160.3, 153.4, 151.5, 151.4, 144.6, 141.0, 139.1, 133.4, 128.2, 125.3, 121.8, 121.1, 117.9, 112.1, 107.4, 61.6, 56.5, 20.9, 20.8, 20.8 ppm.

IR (ATR): $\tilde{\nu}$ = 3071 (w), 2942 (w), 1764 (s), 1719 (s), 1605 (m), 1497 (m), 1423 (m), 1370 (m), 1290 (m), 1206 (s), 1187 (s), 1170 (s), 1094 (s), 1003 (s), 913 (s), 816 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{23}H_{21}O_{10}^{+}$ $[M+H]^{+}$: 457.1129,
found: 457.1134.

6,7-dihydroxy-2*H*-chromen-2-one (esculetin) (71)[30]



1,2,4-Triacetoxybenzene (**69**) (10.0 g, 39.7 mmol, 1 eq.) and malic acid (**70**) (5.85 g, 43.6 mmol, 1.1 eq.) were mixed in solid state and ground. After obtaining a fine powder, conc. H_2SO_4 (16 mL) was added and the resulting mixture was stirred at room temperature. After 10 min, the reaction mixture was heated to 120 °C for 2 h 30 min. The resulting mixture was poured into ice water (200 mL) and was cooled for 10 h at 0 °C. The resulting brown precipitate was collected and the filtrate was extracted with EtOAc (3 × 200 mL). The organic extracts were combined with the filtride and dried (Na_2SO_4). The crude product was purified by flash column

chromatography [CH_2Cl_2:MeOH 19:1] to afford esculetin (**71**) (3.68 g, 52%) as a yellow powder.

R_f: 0.23 (CH_2Cl_2:MeOH 19:1).

mp (MeOH): 268.9 – 271.0 °C.

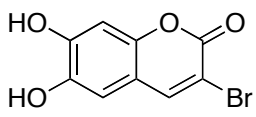
^{1}H NMR (400 MHz, d_6-acetone): δ 8.65 (br, 2H, *O*H), 7.77 (dd, J = 9.6, 0.4 Hz, 1H), 7.05 (s, 1H), 6.77 (d, J = 0.4 Hz, 1H), 6.14 (d, J = 9.6 Hz, 1H) ppm.

^{13}C NMR (100 MHz, d_6-acetone): δ 161.4, 150.7, 150.4, 144.6, 143.4, 113.4, 113.2, 112.5, 103.7 ppm.

IR (ATR): $\tilde{\nu}$ = 3324 (m), 3191 (m), 3059 (m), 1663 (s), 1608 (s), 1566 (s), 1466 (w), 1400 (m), 1388 (m), 1364 (m), 1283 (s), 1198 (m), 1147 (m), 1103 (w), 946 (w), 878 (w), 848 (w), 818 (w), 669 (w), 632 (w) cm^{-1}.

HRMS (ESI): calcd. for $C_9H_5O_4^-$ $[M–H]^-$: 177.0193,
found: 177.0195.

3-bromo-6,7-dihydroxy-2*H*-chromen-2-one (72)



To a stirred solution of esculetin (**71**) (3.08 g, 17.3 mmol, 1 eq.) in acetic acid (70 mL) was added bromine (960 µL, 19.0 mmol, 1.1 eq.) in acetic acid (70 mL) dropwise at 0 °C. After 10 h of stirring at the stated temperature the reaction mixture

was poured into H_2O (100 mL). Reaction mixture was extracted with EtOAc (3 × 120 mL) and the combined organic extractions were washed with sat. aq. NaCl (100 mL). Concentration *in vacuo* and subsequent flash column chromatography [CH_2Cl_2: MeOH 99:1] afforded bromide **72** (3.78 g, 85 %) as pale brown solid.

R_f: 0.24 (CH_2Cl_2: MeOH 15:1).

mp (acetone): 205.9 – 215.7 °C.

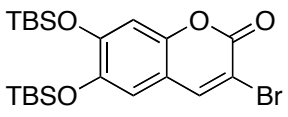
^{1}H NMR (400 MHz, d_6-acetone): δ 8.86 (br, 2H, *O*H), 8.25 (s, 1H), 7.07 (s, 1H), 6.83 (s, 1H) ppm.

^{13}C NMR (100 MHz, d_6-acetone): δ 158.3, 151.7, 150.2, 146.4, 144.4, 113.6, 113.0, 108.1, 104.0 ppm.

IR (ATR): $\tilde{\nu}$ = 3194 (w), 2954 (m), 2869 (m), 1695 (s), 1616 (s), 1550 (s), 1506 (s), 1387 (s), 1277 (s), 1150 (s), 972 (s), 884 (s), 861 (s), 753 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_9H_4BrO_4^-$ $[M–H]^-$: 254.9298,
found: 254.9300.

**3-bromo-6,7-bis((*tert*-butyldimethylsilyl)oxy)-2*H*-chromen-2-one (67)



To a stirred solution of bromo esculetin **72** (2.00 g, 7.78 mmol, 1 eq.) in DMF (40 mL) at 0 °C was added *tert*-butyldimethylsilylchloride (3.52 g, 23.3 mmol, 3.0 eq.), imidazole (2.38 g, 35.0 mmol, 4.5 eq.) and 4-dimethylaminopyridine (0.285 g, 2.33

mmol, 0.3 eq.). The reaction mixture was allowed to come to room temperature and was stirred for additional 3 h. After completion of the reaction, the mixture was diluted with H_2O (50 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (20 mL) and dried (Na_2SO_4). Flash column chromatography [Isohexane: EtOAc 40:1] afforded TBS protected coumarin **67** (3.72 g, 82%) as pale yellow solid.

R_f: 0.36 (Isohexane:EtOAc 10:1).

mp (EtOAc): 160.2 – 163.8°C.

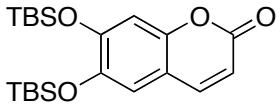
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (s, 1H), 6.82 (s, 2H), 0.99 (s, 9H), 0.99 (s, 9H), 0.26 (s, 6H), 0.21 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7, 151.7, 148.8, 144.8, 144.2, 116.7, 113.1, 108.4, 108.3, 25.8, 25.8, 18.6, 18.4, –4.08, –4.21 ppm.

IR (ATR): $\tilde{\nu}$ = 3052 (w), 2927 (m), 2894 (w), 2856 (w), 1718 (s), 1611 (w), 1545 (m), 1501 (s), 1470 (m), 1361 (s), 1282 (s), 1248 (s), 1156 (s), 973 (s), 885 (s), 837 (s), 777 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{21}H_{34}O_4BrSi_2^+$ $[M+H]^+$: 485.1174,
found: 485.1179.

6,7-bis((*tert*-butyldimethylsilyl)oxy)-2*H*-chromen-2-one (73)



To a stirred solution of esculetin (**71**) (3.50 g, 19.5 mmol, 1 eq.) in DMF (30 mL) was added TBSCl (8.86 g, 58.0 mmol, 3.0 eq.), imidazole (8.00 g, 116 mmol, 6.0 eq.) and 4-dimethylaminopyridine (0.720 g, 5.88 mmol, 30 mol-%) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 3 h. After completion, the reaction mixture was diluted with H_2O (70 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with aq. NaCl (10%, 3 × 50 mL), sat. aq. NaCl (40 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography [Isohexane:EtOAc 30:1] to provide coumarin **73** (7.68 g, 96%) as a pale yellow solid.

R_f: 0.29 (Isohexane:EtOAc 10:1).

mp (EtOAc): 76.8 – 78.6 °C.

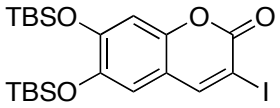
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 9.5 Hz, 1H), 6.85 (s, 1H), 6.82 (s, 1H), 6.25 (d, J = 9.5 Hz, 1H), 1.00 (s, 9H), 0.99 (s, 9H), 0.26 (s, 6H), 0.21 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 151.9, 150.1, 144.8, 143.7, 118.2, 113.1, 112.5, 109.0, 26.4, 26.4, 19.1, 19.0, –3.5, –3.7 ppm.

IR (ATR): $\tilde{\nu}$ = 2955 (m), 2931 (m), 2887 (m), 2362 (w), 2340 (w), 1733 (s), 1617 (m), 1553 (m), 1507 (m), 1472 (m), 1430 (w), 1386 (m), 1363 (w), 1292 (m), 1260 (m), 1233 (w), 1148 (s), 1097 (m), 1006 (w), 943 (m), 888 (m), 831 (m), 783 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{21}H_{35}O_4Si_2^+$ $[M+H]^+$: 407.2068,
found: 407.2067.

6,7-bis((*tert*-butyl(dimethylsilyl)oxy)-3-iodo-2*H*-chromen-2-one (74)



To a stirred $ZnCl_2$ solution (1.0 M in THF, 270 µL, 27 µmol, 0.55 eq.) was added TMP·MgCl·LiCl (1.0 M in THF/toluene, 540 µL, 540 µmol, 1.1 eq.) dropwise at room temperature. The resulting mixture was stirred for 30 min followed by the addition of coumarin **73** (200 mg, 490 µmol, 1 eq.). The mixture was stirred for 7 h 30 min at room temperature. Afterwards iodine solution (1.0 M in THF, 540 µL, 540 µmol, 1.1 eq.) was added and stirred for 15 h at room temperature. The mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with sat. aq. NaCl solution (50 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography [Isohexane: EtOAc 30:1] to provide iodide **74** (130 mg, 50%) as a yellow powder.

R_f: 0.68 (Isohexane: EtOAc 7:1).

mp (EtOAc): 153.3 – 155.1 °C.

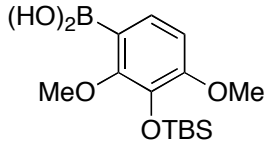
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (s, 1H), 6.83 (s, 2H), 1.02 (s, 9H), 1.01 (s, 9H), 0.29 (s, 6H), 0.23 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1, 152.0, 151.8, 149.6, 144.6, 116.4, 114.1, 108.2, 81.9, 25.8 (2C), 18.6, 18.4, –4.1, –4.2 ppm.

IR (ATR): $\tilde{\nu}$ = 2951 (m), 2928 (s), 2894 (m), 2856 (m), 2360 (w), 2331 (w), 1710 (s), 1613 (w), 1539 (m), 1500 (s), 1471 (m), 1409 (m), 1392 (w), 1361 (m), 1283 (s), 1248 (s), 1181 (m), 1157 (m), 1124 (s), 1000 (w), 963 (m), 919 (m), 886 (m), 836 (s), 806 (m), 778 (s), 748 (m), 680 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{21}H_{34}IO_4Si_2^+$ $[M+H]^+$: 533.1035,
found: 533.1034.

(3-((*tert*-butyldimethylsilyl)oxy)-2,4-dimethoxyphenyl)boronic acid (68)[31]



*a) Synthesis from bromide **75***

To a stirred solution of bromide **75** (300 mg, 0.860 mmol, 1 eq.) in Et_2O (23 mL) was added *t*-BuLi (1.7 M in pentane, 1.00 mL, 1.72 mmol, 2.0 eq-) at –85 °C. The reaction mixture was stirred for 30 min at this temperature. Then triisopropyl borate (300 µL, 1.29 mmol, 1.5 eq.) was added dropwise and the resulting mixture was stirred for 20 min at –85 °C and for additional 20 min at room temperature. During this reaction time a white solid precipitated. The organic solvent was removed *in vacuo* and the residual white solid was hydrolyzed in aq. MeOH (10 mL) on silica gel at 45 °C on a rotary evaporator. Flash column chromatography [Isohexane:EtOAc 10:1 → 4:1] afforded arylboronic acid **76** (226 mg, 84 %) as small colorless needles.

*b) Synthesis by ortho-directed metalation of phenol **178***

To a stirred solution of TMEDA (780 µL, 5.22 mmol, 1.4 eq.) in isohexane (4.5 mL) was added *n*-BuLi (2.5 M in hexane, 1.79 mL, 4.48 mmol, 1.2 eq.) dropwise at 0 °C. The resulting solution was stirred at this temperature for 30 min. Then the solution was cooled down to –14 °C and TBS phenol **178** (1.00 g, 3.73 mmol, 1 eq.) was added slowly over 45 min. After stirring for 1 h at –14 °C the reaction mixture was allowed to warm to room temperature for 18 h followed by the addition of triisopropyl borate (1.19 g, 6.34 mmol, 1.7 eq.) at 0 °C. The resulting solution was stirred for 20 min at 0 °C and for 20 min at room temperature. Subsequently the

reaction mixture was diluted with sat. aq. NH_4Cl (20 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with sat. aq. NaCl solution (15 mL) and dried ($MgSO_4$). Flash column chromatography [Isohexane: EtOAc 8:1] afforded arylboronic acid **68** (180 mg, 15 %) as small colorless needles.

R_f: 0.35 (Isohexane:EtOAc 4:1).

mp (EtOAc): 112.3 – 113.8 °C.

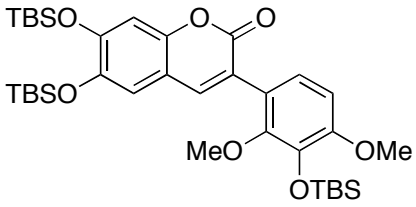
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, J = 8.3 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 5.88 (br, 2 *O*H), 3.90 (s, 3H), 3.85 (s, 3H), 1.05 (s, 9H), 0.16 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 154.9, 137.2, 128.4, 114.9, 107.7, 61.0, 76.6, 25.8, 18.6, –4.6 ppm.

IR (ATR): $\tilde{\nu}$ = 3475 (m), 3377 (m), 3209 (m), 2999 (w), 2947 (m), 2927 (s), 2895 (m), 2857 (m), 1593 (m), 1502 (m), 1459 (s), 1425 (s), 1361 (m), 1339 (s), 1299 (m), 1250 (m), 1234 (m), 1214 (m), 1091 (s), 1053 (m), 1008 (m), 956 (m), 911 (m), 831 (s), 814 (m), 785 (m), 778 (m), 752 (m), 677 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{14}H_{26}BO_7Si^-$ [M+formiat]$^-$: 357.1546,
found: 357.1545.

6,7-bis((*tert*-butyldimethylsilyl)oxy)-3-(3´-((*tert*-butyldimethylsilyl)oxy)-2´,4´-dimethoxyphenyl)-2*H*-chromen-2-one (66)



To a stirred solution of coumarin **73** (1.06 g, 2.60 mmol, 1.3 eq.) in toluene (10 mL) was added freshly prepared $TMP_2Zn•MgCl_2•2LiCl$ solution[4a] (0.37 M in THF, 3.90 mL, 1.45 mmol, 0.73 eq.) dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. After complete zincation, the reaction solution was degassed and a degassed solution of bromide **75** (659 mg, 2.00 mmol, 1 eq.) in toluene (5 mL) was added. After subsequent addition of $Pd(OAc)_2$ (23.0 mg, 100 µmol, 5 mol-%) and SPhos (82.0 mg, 200 µmol, 10 mol-%), the reaction mixture was heated to 65 °C for 2 h. After completion, sat. aq. NH_4Cl (15 mL) was added and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with sat. aq. NaCl (20 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 50:1] to afford coumarin **66** (1.13 g, 84%) as a pale white solid.

R_f: 0.57 (Isohexane:EtOAc 7:1).

mp (EtOAc): 54.1 – 56.8 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 (s, 1H), 6.96 (d, J = 8.6 Hz, 1H), 6.87 (s, 1H), 6.84 (s, 1H), 6.66 (d, J = 8.6 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 1.02 (s, 9H), 0.99 (s, 18H), 0.26 (s, 6H), 0.20 (s, 6H), 0.17 (s, 6H) ppm.

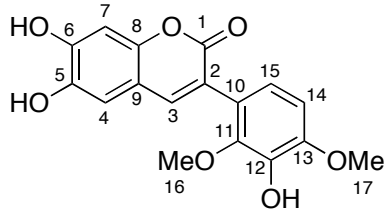
^{13}C NMR (150 MHz, $CDCl_3$): δ 161.9, 152.8, 150.7, 150.2, 149.5, 144.6, 141.9, 138.9, 122.9, 122.6, 122.1, 118.1, 113.8, 108.6, 107.3, 60.9, 55.8, 26.3 (2C), 26.3,

19.1, 19.1, 18.9, –3.6, –3.8, –4.1 ppm.

IR (ATR): $\tilde{\nu}$ = 2953 (s), 2930 (s), 2897 (m), 2858 (s), 1730 (m), 1615 (w), 1564 (w), 1499 (m), 1462 (m), 1427 (m), 1372 (w), 1327 (w), 1253 (m), 1205 (w), 1161 (w), 1127 (w), 1095 (m), 1007 (w), 950 (m), 917 (w), 837 (m), 803 (m), 779 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{35}H_{57}O_7Si_3^+$ $[M+H]^+$: 673.3407,
found: 673.3406.

santalin AC (21)



santalin AC

a) *deprotection from acetoxy santalin AC* ***65***

To a stirred solution of acetoxy-coumarin **65** (20.0 mg, 44.0 µmol, 1 eq.) in MeOH (1 mL) was added aq. HCl (2 M, 2 mL) at room temperature. Reaction mixture was heated to 100 °C for 1 h 30 min. After completion, the reaction mixture was cooled to 0 °C. After 1 h the formed precipitate was collected by sedimentation with a centrifuge and washed with MeOH (2 × 0.5 mL), which afforded santalin AC (**21**) (13.0 mg, 89%) as a yellow powder.

b) deprotection from TBS santalin AC ***66***

To a stirring solution of TBS-coumarin **66** (100 mg, 148 µmol, 1 eq.) in THF (3 mL) was added TBAF (1 M solution in THF, 488 µL, 488 µmol, 3.3 eq.) at 0 °C. Reaction

mixture was stirred at this temperature for 20 min. After completion, H_2O (4 mL) was added and the biphasic mixture was extracted with EtOAc (2 × 7 mL). The combined organic extracts were washed with sat. aq. NaCl (3 mL) and dried (Na_2SO_4). The crude product was purified by precipitation with MeOH (1 mL). The precipitate was collected by sedimentation using a centrifuge. Purification was achieved by washing the precipitate with MeOH (2 × 0.3 mL), which afforded santalin AC (**21**) (31.0 mg, 63%) as a yellow powder.

R_f: 0.13 (CH_2Cl_2:MeOH 10:1).

mp (MeOH): 289 °C decomp.

^{1}H NMR (400 MHz, d_6-DMSO): δ 10.18 (s, 1H, *O*H), 9.39 (s, 1H, *O*H), 8.73 (s, 1H, *O*H), 7.75 (s, 1H), 7.00 (s, 1H), 6.77 (s, 1H), 6.76 (d, J = 8.5 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 3.81 (s, 3H), 3.64 (s, 3H) ppm.

^{13}C NMR (100 MHz, d_6-DMSO): δ 160.8, 150.3, 149.5, 148.4, 146.5, 143.2, 142.2, 139.5, 122.9, 121.9, 120.3, 112.7, 111.7, 107.3, 102.7, 60.1, 56.4 ppm.

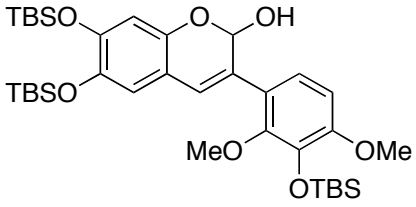
IR (ATR): $\tilde{\nu}$ = 2960 (m), 2875 (w), 1730 (s), 1573 (m), 1462 (m), 1372 (m), 1289 (m), 1238 (s), 1089 (s), 1044 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{17}H_{15}O_7^+$ $[M+H]^+$: 331.0812,
found: 331.0811.

Number	^{1}H (synthetic)	^{13}C (Synthetic)	^{1}H (Isolated)[2]	^{13}C (Isolated)[2]
*O*H	10.18 (s)		-	
*O*H	9.39 (s)		-	
*O*H	8.73 (s)		-	
1		160.8		160.3
2		121.9		122.3
3	7.75 (s, 1H)	142.2	7.73 (s, 1H)	141.7
4	7.00 (s, 1H)	112.7	7.00 (s, 1H)	111.9
5		143.2		143.6
6		150.3		151.5
7	6.77 (s, 1H)	102.7	6.67 (s, 1H)	99.7
8		148.4		147.9

9		111.7		112.0
10		122.9		122.4
11		146.5		146.1
12		139.5		139.1
13		149.5		149.2
14	6.76 (d, *J* = 8.5 Hz, 1H)	107.3	6.75 (d, *J* = 8.5 Hz, 1H)	106.9
15	6.71 (d, *J* = 8.5 Hz, 1H)	120.3	6.71 (d, *J* = 8.5 Hz, 1H)	119.8
16	3.64 (s, 3H)	60.1	3.64 (s, 3H)	-
17	3.81 (s, 3H)	56.4	3.81 (s, 3H)	-

6,7-bis((*tert*-butyldimethylsilyl)oxy)-3-(3′-((*tert*-butyldimethylsilyl)oxy)-2′,4′-dimethoxyphenyl)-2*H*-chromen-2-ol (82)



To a stirred solution of coumarin **66** (2.02 g, 3.00 mmol, 1 eq.) in CH_2Cl_2 (20 mL) was added DIBAL-H (1 M solution in CH_2Cl_2, 3.15 mL, 3.15 mmol, 1.05 eq.) dropwise (3 mL/h) at –78 °C and the reaction mixture was stirred for 1 h at this temperature. After completion, H_2O (10 mL) was added at –78 °C and was allowed to warm to room temperature over a period of 20 min. The resulting slurry was extracted with Et_2O (3 × 40 mL) the combined organic extracts were washed with sat. aq. NaCl solution (50 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 15:1] to provide **82** (1.72 g, 85%) as a pale yellow foam.

Slow addition of DIBAL-H to a vigorously stirring solution is necessary, otherwise overreduction takes place!

R_f: 0.30 (Isohexane:EtOAc 10:1).

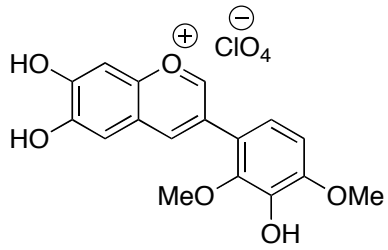
^{1}H NMR (600 MHz, d_3-MeCN): δ 6.97 (d, J = 6.9 Hz, 1H), 6.92 (d, J = 6.9 Hz, 1H), 6.81 (s, 1H), 6.79 (s, 1H), 6.79 (s, 1H), 6.08 (d, J = 6.0 Hz, 1H), 3.77 (s, 3H), 3.61 (s, 3H), 1.00 (s, 9H), 0.97 (s, 9H), 0.96 (s, 9H), 0.18 (s, 6H), 0.14 (s, 6H), 0.11 (s, 6H) ppm.

^{13}C NMR (150 MHz, d_3-MeCN): δ 151.5, 149.8, 146.8, 145.0, 140.7, 138.2, 129.4, 124.7, 122.3, 121.6, 118.6, 115.8, 108.9, 108.0, 91.5, 60.3, 55.9, 26.2, 26.2, 26.1, 18.8, 18.5, 18.5, –3.7, –3.8, –3.8, –3.8, –4.1, –4.2 ppm.

IR (ATR): $\tilde{\nu}$ = 2952 (w), 1613 (w), 1570 (w), 1292 (m), 1252 (m), 1203 (w), 1165 (w), 1040 (w), 988 (m), 777 (s), 682 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{35}H_{57}O_6Si_3^+$ $[M–OH]^+$: 657.3457,
found: 657.3463.

6,7-dihydroxy-3-(3-hydroxy-2,4-dimethoxyphenyl)chromenylium perchlorate (83)



To a stirred solution of lactol **82** (500 mg, 740 µmol, 1 eq.) in acetic acid (5 mL) was added perchloric acid (aq. 65 %, 408 µL, 4.39 mmol, 6 eq.) at room temperature. The reaction mixture was stirred for 8 h, upon which precipitation started. After stirring

for an additional 1 h at room temperature, the reaction mixture was transferred into a falcon tube. The precipitate was collected by sedimentation using a centrifuge. Purification was achieved by washing the precipitate with CH_2Cl_2 (2 × 0.5 mL), which afforded isoflavylium salt **83** (234 mg, 76%) as a pale orange powder.

X-ray quality crystals were obtained by dissolving the orange salt in MeCN and then adding AcOH (1:1), followed by slow evaporation of the solvent at room temperature over time.

Precipitation can be forced by addition of isoflavylium salt or scratching at glass wall!

R_f: 0.50 (CH_2Cl_2:MeOH 10:1).

UV (MeOH): λ_{max} = 395 nm.

mp (AcOH/MeCN): 189.3 – 190.7 °C.

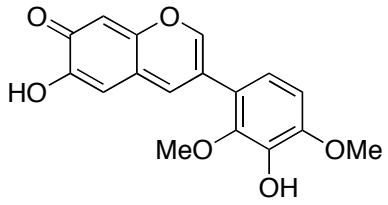
^{1}H-NMR (400 MHz, d_3-MeCN): δ 9.85 (s, 1H, *O*H), 9.41 (d, *J* = 2.1 Hz, 1H), 9.29 (ddd, *J* = 2.1, 0.8, 0.4 Hz, 1H), 8.84 (s, 1H, *O*H) 7.63 (d, *J* = 0.8 Hz, 1H), 7.62 (s, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.85 (s, 1H, *O*H), 3.95 (s, 3H), 3.74 (s, 3H) ppm.

^{13}C NMR (100 MHz, d_3-MeCN): δ 162.7, 162.5, 157.3, 154.4, 151.4, 150.8, 146.2, 140.9, 129.9, 124.6, 121.4, 119.3, 111.3, 109.3, 104.0, 61.8, 57.5 ppm.

IR (ATR): $\tilde{\nu}$ = 3246 (w), 2348 (s), 1741, 1573 (s), 1408 (s), 1286 (s), 1100 (s), 1071 (s), 824 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{17}H_{15}O_6^+$ $[M–ClO_4]^+$: 315.0863,
found: 315.0865.

6-hydroxy-3-(3-hydroxy-2,4-dimethoxyphenyl)-7*H*-chromen-7-one (30)



To a stirred solution of isoflavylium perchlorate **83** (500 mg, 1.33 mmol, 1 eq.) in degassed MeCN (13 mL) was added di-*tert*-butylpyridine (320 µL, 1.40 mmol, 1.05 eq.) in one portion at 0 °C. The reaction was stirred for 10 min, whereupon product precipitated. Reaction was stirred for 1 h and the precipitate was collected by sequential transfer into a falcon tube and by subsequent sedimentation in a centrifuge. The crude product was purified by washing the precipitate with cold MeCN (2 × 0.5 mL), which afforded anhydrobase **30** (372 mg, 89%) as an orange powder.

R_f: 0.48 (CH_2Cl_2:MeOH 10:1).

UV (MeOH): λ_{max} = 441 nm.

mp (MeCN): 168.7 – 170.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 1.7 Hz, 1H), 7.86 (ddd, J = 1.7, 1.1, 0.5 Hz, 1H), 6.83 (d, J = 0.5 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 6.74 (d, J = 8.6 Hz, 1H), 6.67 (d, J = 1.1 Hz, 1H), 3.95 (s, 3H), 3.77 (s, 3H) ppm.

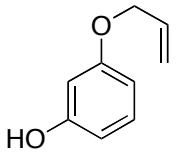
^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 158.9, 152.9, 148.6, 147.5, 144.8, 139.3, 137.4, 123.8, 120.5, 120.4, 119.5, 107.0, 102.8, 101.4, 60.9, 56.6 ppm.

IR (ATR): $\tilde{\nu}$ = 3447 (w), 3382 (w), 3089 (w), 2348 (w), 1525 (s), 1373 (s), 1283 (s), 1052 (s), 851 (s), 808 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{17}H_{15}O_6^+$ $[M+H]^+$: 315.0863,
found: 315.0865.

V. 4. Experimental towards santalin Y and santalin Y benzoxanthenone

3-(allyloxy)phenol (87)[55]



To a stirred solution of resorcinol (**86**) (9.36 g, 85.0 mmol, 1 eq.) in DMF (50 mL) was added successively anhydrous K_2CO_3 (11.8 g, 85.0 mmol, 1 eq.) and potassium iodide (2.82 g, 17.0 mmol, 0.2 eq.). After stirring for 10 min, allylbromide (7.35 mL, 85 mmol, 1 eq.) was added at room temperature. The reaction mixture was stirred for 12 h and after completion, sat. aq. NH_4Cl (150 mL) was added and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were washed with sat. aq. NaCl (40 mL) and dried (Na_2SO_4). Flash column chromatography [Isohexane:EtOAc 16:1 → 8:1] afforded mono allyl protected resorcinol **87** (5.73 g, 45 %) as a pale yellow oil.

R_f: 0.14 (Isohexane:EtOAc 10:1).

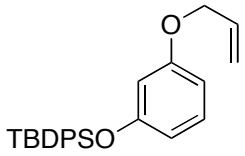
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (t, J = 8.3 Hz, 1H), 6.51 (ddd, J = 8.3, 2.2, 1.0 Hz, 1H), 6.46 – 6.39 (m, 2H), 6.15 – 5.94 (m, 1H), 5.41 (dq, J = 17.3, 1.5 Hz, 1H), 5.29 (dq, J = 17.3, 1.5 Hz, 1H), 4.71 (s, 1H, O*H*), 4.51 (dt, J = 5.3, 1.5 Hz, 2H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.2, 156.8, 133.4, 130.3, 117.9, 108.1, 107.5, 102.6, 69.1 ppm.

IR (ATR): $\tilde{\nu}$ = 3375 (br), 3081 (w), 2983 (w), 2919 (w), 1592 (s), 1489 (s), 1456 (s), 1422 (m), 1278 (s), 1171 (s), 1141 (s), 1022 (s), 993 (s), 925 (s), 827 (s), 759 (s) cm^{-1}.

HRMS (EI): calc. for $C_9H_{10}O_2$ $[M^{\bullet}]^+$: 150.0675,
found: 150.0677.

(3-(allyloxy)phenoxy)(*tert*-butyl)diphenylsilane (88)[36]



To a stirred mixture of allyl resorcinol **87** (2.02 g, 13.4 mmol, 1 eq.) and DMF (20 mL) was added successively imidazole (1.54 g, 22.6 mmol, 1.7 eq.), and TBDPSCl (4.39 g, 16.0 mmol, 1.3 eq.). The reaction mixture was warmed to room temperature and stirred for additional 2 h. After completion H_2O (30 mL) was added and was extracted with Et_2O (4 × 40 mL), the organic extracts were washed with aq. NaCl (10%, 2 × 20 mL), sat. aq. NaCl (10 mL) and were dried ($MgSO_4$). Purification of the crude product by flash column chromatography [Isohexane] afforded **88** (5.11 g, 99%) as a colorless oil.

R_f: 0.74 (Isohexane:EtOAc 10:1).

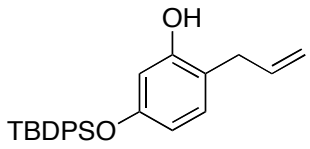
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 – 7.70 (m, 4H), 7.45 – 7.32 (m, 6H), 6.96 (t, J = 8.3 Hz, 1H), 6.45 (ddd, J = 8.3, 2.2, 1.1 Hz, 1H), 6.38 – 6.35 (m, 2H), 5.92 (ddt, J = 17.2, 10.6, 5.3 Hz, 1H), 5.27 (dq, J = 17.2, 1.6 Hz, 1H), 5.18 (dq, J = 10.6, 1.4 Hz, 1H), 4.29 (dt, J = 5.4, 1.5 Hz, 2H), 1.10 (s, 9H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 156.9, 135.8, 133.4, 133.2, 130.1, 129.7, 128.0, 117.7, 112.6, 108.2, 106.7, 68.9, 26.8, 19.7 ppm.

IR (ATR): $\tilde{\nu}$ = 3049 (w), 3070 (w), 2956 (w), 2930 (w), 2857 (w), 1593 (s), 1488 (s), 1427 (s), 1289 (s), 1266 (s), 1175 (s), 1145 (s), 1112 (s), 1105 (s), 997 (s), 967 (s), 925 (s), 834 (s), 821 (s), 698 (s) cm^{-1}.

HRMS (EI): calc. for $C_{25}H_{28}O_2Si^+$ $[M^\bullet]^+$: 388.1853,
found: 388.1860.

2-allyl-5-((*tert*-butyldiphenylsilyl)oxy)phenol (91)[36]



To a stirred solution of allyl ether **88** (999 mg, 2.68 mmol, 1 eq.) in *n*-hexane (10 mL) was added dropwise Et_2AlCl (1 M in hexane, 5.36 mL, 5.36 mmol, 2 eq.) at 0 °C. After stirring for 50 min at 0 °C and 2 h at room temperature the mixture was cooled to 0 °C, acidified dropwise with aq. HCl (2 M, 20 mL) and extracted with Et_2O (3 × 60 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Isohexane: EtOAc 40:1] afforded **91** (632 mg, 64%) as a colorless oil.

R_f: 0.25 (Isohexane:EtOAc 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 – 7.70 (m, 4H), 7.42 – 7.34 (m, 6H), 6.78 (d, J = 8.6 Hz, 1H), 6.30 – 6.27 (m, 2H), 5.96 – 5.91 (m, 1H), 5.10 (t, J = 1.5 Hz, 1H), 5.07

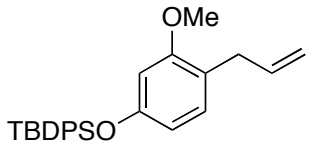
(dq, J = 6.3, 1.6 Hz, 1H), 4.72 (s, 1H, *O*H), 3.27 (dt, J = 6.3, 1.6 Hz, 2H), 1.08 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 154.7, 137.0, 135.7, 133.2, 130.7, 130.1, 128.0, 118.0, 116.3, 112.5, 107.7, 34.8, 26.7, 19.7 ppm.

IR (ATR): $\tilde{\nu}$ = 3070 (w), 3957 (w), 2930 (m), 2857 (m), 1594 (s), 1488 (s), 1427 (s), 1289 (s), 1266 (s), 1175 (s), 1145 (s), 1112 (s), 997 (s), 821 (s), 698 (s) cm^{-1}.

HRMS (ESI): calc. for $C_{25}H_{27}O_2Si^-$ $[M–H]^-$: 387.1786,
found: 387.1780.

(4-allyl-3-methoxyphenoxy)(*tert*-butyl)diphenylsilane (92)



To a stirred solution of phenol **91** (8.60 g, 22.1 mmol, 1 eq.) in CH_2Cl_2 (120 mL) were added molecular sieve 4Å (11 g), proton sponge (7.19 g, 53.0 mmol, 2.2 eq.) and trimethyloxonium tetrafluoroborate (11.4 g, 48.6 mmol, 2.2 eq.). After stirring for 7 h at room temperature the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. Flash column chromatography [Isohexane: EtOAc 100:0 → 99:1] afforded **92** (2.39 g, 80 %) as a colorless oil.

R_f: 0.69 (Isohexane:EtOAc 10:1).

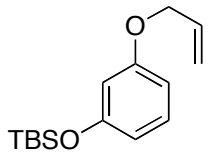
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 – 7.70 (m, 4H), 7.46 – 7.33 (m, 6H), 6.81 (d, J = 8.1 Hz, 1H), 6.31 (dd, J = 8.1, 2.3 Hz, 1H), 6.26 (d, J = 2.3 Hz, 1H), 5.92 (m, 1H), 5.01 – 4.92 (m, 2H), 3.50 (s, 3H), 3.23 (d, J = 6.7 Hz, 2H), 1.11 (s, 9H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 155.2, 137.6, 135.7, 133.3, 130.0, 129.8, 127.9, 121.1, 115.0, 111.4, 103.3, 55.3, 33.7, 26.8, 19.7 ppm.

IR (ATR): $\tilde{\nu}$ = 3071 (w), 2998 (w), 2955 (m), 2930 (m), 2856 (m), 1606 (s), 1584 (s), 1502 (s), 1427 (s), 1290 (s), 1199 (s), 1159 (s), 1112 (s), 979 (s), 820 (s), 697 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{26}H_{31}O_2Si^+$ $[M+H]^+$: 403.2088,
found: 403.2089.

(3-(allyloxy)phenoxy)(*tert*-butyl)dimethylsilane (181)[56]



To a stirred mixture of allyl resorcinol **87** (3.00 g, 20.0 mmol, 1 eq.) and DMF (25 mL) was added successively imidazole (3.54 g, 52.0 mmol, 2.6 eq.), and TBSCl (3.92 g, 26.0 mmol, 1.3 eq.). The mixture was warmed to room temperature and stirred for 2 h. After completion H_2O (30 mL) was added and was extracted with Et_2O (4 × 40 mL), the organic extracts were washed with aq. NaCl (10% w/v, 2 × 20 mL) and sat. aq. NaCl (10 mL) and dried ($MgSO_4$). Purification of the crude product by flash column chromatography [Isohexane] afforded **181** (4.75 g, 90%) as a colorless oil.

R_f: 0.69 (Isohexane:EtOAc 10:1).

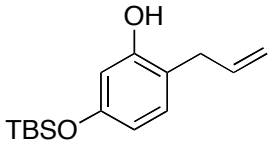
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (t, J = 7.9 Hz, 1H), 6.56 – 6.39 (m, 3H), 6.13 – 5.95 (m, 1H), 5.40 (dq, J = 17.3, 1.6 Hz, 1H), 5.28 (dq, J = 10.5, 1.4 Hz, 1H), 4.51 (t, J = 1.7 Hz, 1H), 4.49 (t, J = 1.7 Hz, 1H0.98 (s, 9H), 0.20 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 157.0, 133.6, 129.9, 117.8, 113.0, 107.9, 107.4, 69.1, 25.9, 18.4, –4.2 ppm.

IR (ATR): $\tilde{\nu}$ = 2955 (m), 2928 (m), 2884 (w), 2857 (m), 1593 (s), 1488 (s), 1471 (s), 1287 (s), 1257 (s), 1174 (s), 1144 (s), 998 (m), 834 (s), 778 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{15}H_{24}O_2Si^+$ $[M^\bullet]^+$: 264.1540,
found: 264.1525.

2-allyl-5-(*tert*-butyldimethylsilyloxy)phenol (182)[36]



To a stirred solution of allyl ether **181** (2.43 g, 9.20 mmol, 1 eq.) in *n*-hexane (41 mL) was added dropwise Et_2AlCl (1 M in hexane, 20.2 mmol, 20.2 mL, 2.2 eq.) at 0 °C. After stirring for 30 min at 0 °C and for 2 h at room temperature the mixture was cooled to 0 °C, acidified dropwise with aq. HCl (2 M, 10 mL) and extracted with Et_2O (3 × 250 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Isohexane: EtOAc 45:1] afforded **182** (2.85 g, 59%) as a colorless oil.

R_f: 0.62 (Isohexane:EtOAc 7:1).

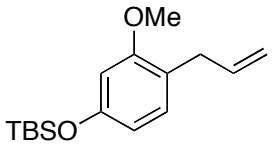
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (d, J = 6.9 Hz, 1H), 6.40 – 6.35 (m, 2H), 6.04 – 5.95 (m, 1H), 5.18 – 5.13 (m, 2H), 4.86 (s, 1H, *O*H), 3.33 (d, J = 3.3 Hz, 2H), 0.97 (s, 9H), 0.19 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 154.8, 136.8, 130.6, 117.8, 116.2, 112.6, 108.0, 34.7, 25.7, 18.2, –4.4 ppm.

IR (ATR): $\tilde{\nu}$ = 3077 (w), 2955 (w), 1638 (m), 1614 (w), 1590 (w), 1292 (m), 1254 (m), 986 (s), 866 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{15}H_{25}O_2Si^+$ $[M+H]^+$: 265.1618,
found: 265.1627.

(4-allyl-3-methoxyphenoxy)(*tert*-butyl)dimethylsilane (183)



To a stirred solution of phenol **182** (2.85 g, 10.8 mmol, 1 eq.) in CH_2Cl_2 (50 mL) were added molecular sieve 4Å (5.5 g), proton sponge (5.70 g, 26.9 mmol, 2.5 eq.) and trimethyloxonium tetrafluoroborate (3.50 g, 23.7 mmol, 2.2 eq.). After stirring for 4 h at room temperature the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. Flash column chromatography [Isohexane] afforded **183** (2.39 g, 80%) as a colorless oil.

R_f: 0.63 (Isohexane: EtOAc 30:1).

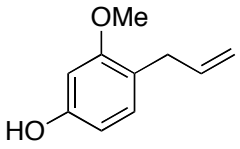
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.94 (d, J = 7.0 Hz, 1H), 6.39 (d, J = 6.3 Hz, 1H), 6.37 (s, 1H), 6.02 – 5.92 (m, 1H), 5.04 – 5.02 (m, 1H), 4.99 (t, J = 1.4 Hz, 1H), 3.78 (s, 3H), 3.30 (d, J = 3.3 Hz, 2H), 0.99 (s, 9H), 0.20 (s, 6H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ 157.9, 155.1, 137.5, 129.8, 121.3, 114.9, 111.4, 103.5, 55.4, 33.6, 25.7, 18.2, –4.4 ppm.

IR (ATR): $\tilde{\nu}$ = 2955 (w), 1638 (w), 1502 (s), 1289 (m), 1255 (m), 1199 (s), 1039 (m), 977 (s), 777 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{16}H_{27}O_2Si^+$ $[M+H]^+$: 279.1775,
found: 279.1782.

4-allyl-3-methoxyphenol (84)[57]



To a stirred solution of TBS protected phenol **183** (2.40 g, 8.6 mmol, 1 eq.) in THF (1 mL) was added TBAF (1 M solution in THF, 9.30 mL, 9.30 mmol, 1.1 eq.) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. After completion, reaction mixture was diluted with H_2O (10 mL) and was extracted with Et_2O (3 × 15 mL). The crude product was purified by flash column chromatography [Isohexane/EtOAc 7:1] to afford **84** (1.00 g, 85%) of the pure product as a colorless oil.

R_f: 0.16 (Isohexane:EtOAc 10:1)

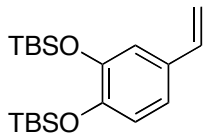
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (d, J = 6.9 Hz, 1H), 6.39 (d, J = 6.4 Hz, 1H), 6.34 (dd, J = 6.4 Hz, 1H), 6.02 – 5.90 (m, 1H), 5.03 – 5.02 (m, 1H), 4.99 (t, 1H), 3.79 (s, 3H), 3.29 (d, J = 3.3 Hz, 2H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2, 155.0, 137.3, 130.1, 120.8, 114.9, 106.5, 98.8, 55.4, 33.5 ppm.

IR (ATR): $\tilde{\nu}$ = 3325 (m), 3076 (w), 2935 (w), 1638 (w), 1597 (s), 1505 (s), 1277 (m), 1234 (w), 1199 (s), 1152 (s), 827 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{10}H_{12}O_2^+$ $[M+H]^+$: 164.0837,
found: 164.0832.

(4-vinyl-1,2-phenylene)bis(oxy)bis(*tert*-butyldimethylsilane) (94)[58]



To a stirred solution of methyltriphenylphosphoniumbromide (1.08 g, 3.03 mmol, 1.1 eq.) in THF (20 mL) was added *n*-BuLi (2.4 M in hexanes, 1.25 mL, 3.00 mmol, 1.1 eq.) followed by dropwise addition of aldehyde **61** (1.00 g, 2.73 mmol, 1 eq.). After 4 h sat. aq. NH_4Cl (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Isohexane] afforded styrene **94** (618 mg, 62%) as a pale yellow oil.

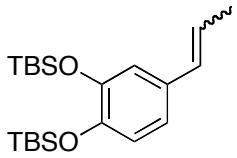
R_f: 0.76 [Isohexane: EtOAc 16:1].

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90 (d, J = 2.2 Hz, 1H), 6.86 (ddd, J = 8.2, 2.2, 0.4 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.59 (ddd, J = 17.6, 10.8, 0.4 Hz, 1H), 5.54 (dd, J = 17.6, 1.0 Hz, 1H), 5.10 (dd, J = 10.8, 1.0 Hz, 1H), 1.00 (s, 9H), 0.99 (s, 9H), 0.21 (s, 6H), 0.20 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 147.1, 147.0, 136.6, 131.5, 121.1, 119.8, 118.9, 111.8, 26.1, 26.1, 18.7, 18.6, –3.9, –3.9 ppm.

HRMS (ESI): calcd. for $C_{20}H_{37}O_2Si_2^+$ $[M+H]^+$: 365.2327,
found: 365.2326.

(4-(prop-1-enyl)-1,2-phenylene)bis(oxy)bis(*tert*-butyldimethylsilane) (93)



To a stirred solution of ethyltriphenylphosphonium bromide (1.12 g, 3.03 mmol, 1.1 eq.) in THF (20 mL) was added *n*-BuLi (2.4 M solution in hexanes, 1.25 mL, 3.00 mmol, 1.1 eq.) followed by dropwise addition of aldehyde **61** (1.00 g, 2.73 mmol, 1 eq.). After 4 h sat. aq. NH_4Cl (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography [Isohexane] afforded an inseparable mixture of *E* and *Z* isomers (1.7:1) of **93** (652 mg, 63%) as a pale yellow oil.

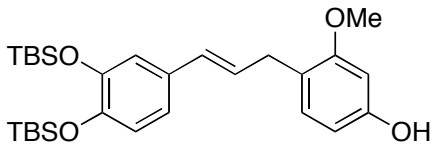
R_f: 0.74 (Isohexane: EtOAc 16:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84 – 6.71 (m, 6H), 6.30 (dq, J = 11.6, 1.8 Hz, 1H), 6.27 (dq, J = 15.7, 1.6 Hz, 1H), 6.03 (dq, J = 15.7, 6.6 Hz, 1H), 5.66 (dq, J = 11.6, 7.2 Hz, 1H), 1.89 (dd, J = 7.2, 1.8 Hz, 3H), 1.84 (dd, J = 6.6, 1.6 Hz, 3H), 0.99 (s, 9H), 0.99 (s, 9H), 0.99 (s, 9H), 0.98 (s, 9H), 0.21 (s, 6H), 0.20 (s, 6H), 0.20 (s, 6H), 0.19 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 146.9, 146.5, 146.1, 145.6, 131.8, 131.4, 130.7, 129.7, 125.1, 123.7, 122.4, 121.7, 121.1, 120.8, 119.2, 118.6, 26.1, 26.1, 18.6, 18.5, –3.9, –3.9 ppm.

HRMS (ESI): calcd. for $C_{21}H_{39}O_2Si_2^+$ $[M+H]^+$: 379.2483,
found: 379.2482.

(*E*)-4-(3-(3,4-bis(*tert*-butyldimethylsilyloxy)phenyl)allyl)-3-methoxyphenol (96)



To a stirred solution of allylphenol **84** (1.00 g, 6.09 mmol, 1 eq.) and styrene **93** (2.30 g, 6.09 mmol, 1 eq.) in CH_2Cl_2 (15 mL) was added Grubbs II catalyst (258 mg, 0.31 mmol, 6 mol-%). The reaction mixture was stirred for 7 h at 50 °C in a pressure tube. After completion, the reaction mixture was concentrated in vacuo. The crude product was purified by flash column chromatography [Isohexane: EtOAc 12:1] to give benzylstyrene **96** (1.89 g, 62%) as a pale yellow oil.

R_f = 0.43 (Isohexane:EtOAc 30:1).

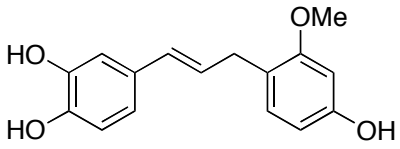
^{1}H NMR (400 MHz, CD_2Cl_2): δ 6.99 (d, J = 8.1 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.81 (dd, J = 8.2, 2.1 Hz, 1H), 6.75 (dd, J = 8.2, 0.6 Hz, 1H), 6.42 (d, J = 2.2 Hz, 1H), 6.35 (ddd, J = 8.1, 2.4, 1.0 Hz, 1H), 6.27 (d, J = 15.9 Hz, 1H), 6.16 (dtd, J = 15.7, 6.5, 1.0 Hz, 1H), 4.98 (s, 1H, *O*H), 3.80 (s, 3H), 3.39 (d, J = 6.5 Hz, 2H), 0.99 (s, 9H), 0.98 (s, 9H), 0.20 (s, 6H), 0.19 (s, 6H) ppm.

^{13}C NMR (100 MHz, CD_2Cl_2): δ 158.9, 156.0, 147.4, 146.7, 132.2, 130.7, 130.4, 127.9, 121.6, 121.5, 119.8, 119.2, 107.1, 99.4, 56.0, 33.2, 26.3, 26.3, 19.0, 18.9, –3.8, –3.8 ppm.

IR (ATR): $\tilde{\nu}$ = 3407 (w), 2956 (w), 2929 (w), 1615 (w), 1597 (w), 1507 (s), 1287 (s), 1251 (s), 1238 (s), 1041 (m), 866 (s), 779 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{28}H_{44}O_4Si_2^+$ $[M+H]^+$: 500.2778,
found: 500.2861.

(*E*)-4-(3-(4-hydroxy-2-methoxyphenyl)prop-1-enyl)benzene-1,2-diol (27)



To a stirred solution of benzylstyrene **96** (260 mg, 0.600 mmol, 1 eq.) in THF (10 mL) was added TBAF (1.0 M solution in THF, 1.20 mL, 1.20 mmol, 2 eq.) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. After completion, the reaction mixture was added H_2O (10 mL) and was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography [CH_2Cl_2:MeOH 97:3] to give **27** (112 mg, 69%) of the product as a pale red oil.

R_f: 0.21 (CH_2Cl_2: MeOH 20:1).

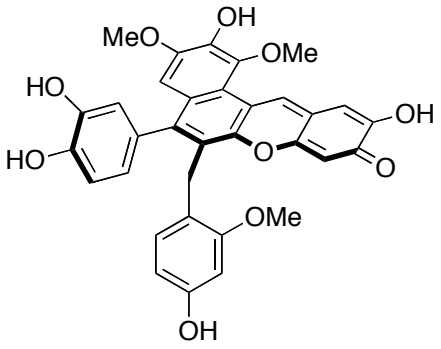
^{1}H NMR (400 MHz, d_3-MeCN): δ 6.95 (d, J = 8.1 Hz, 1H), 6.84 (s, 1H), 6.71 (s, 2H), 6.43 (d, J = 2.3 Hz, 1H), 6.34 (dd, J = 8.1, 2.4 Hz, 1H), 6.25 (d, J = 15.9 Hz, 1H), 6.14 (dt, J = 15.9, 6.6 Hz, 1H), 3.78 (s, 3H), 3.34 (d, J = 6.5 Hz, 2H) ppm.

^{13}C NMR (100 MHz, d_3-MeCN): δ 159.6, 158.0, 146.0, 145.2, 132.0, 131.5, 131.1, 128.3, 121.3, 119.8, 116.6, 113.8, 108.0, 100.3, 56.4, 33.6 ppm.

IR (ATR): $\tilde{\nu}$ = 3295 (s), 2941 (m), 2834 (m), 1597 (s), 1507 (s), 1278 (s), 1243 (m), 1194 (s), 1109 (s), 1041 (s), 785 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{16}H_{16}O_4^+$ $[M+H]^+$: 272.1049,
found: 272.1125.

santalin Y benzoxanthenone isomer (97)



Benzylstyrene **27** (4.00 mg, 14.0 µmol, 1 eq.) and anhydrobase **30** (5.00 mg, 14.0 µmol, 1 eq.) were dissolved in MeOH (0.5 mL). The reaction vessel was sealed and was heated for 12 h. After this time, the reaction mixture was concentrated *in vacuo*. Purification by sephadex column chromatography (LH-20, MeOH) afforded benzoxanthenone **97** (3.00 mg, 36%) as a dark red oil.

R_f: 0.16 (CH_2Cl_2: MeOH 10:1).

UV (MeCN): λ_{max} = 441, 467, 499 nm.

^{1}H NMR (600 MHz, d_6-DMSO): δ 9.62 (br, 1H, *O*H), 9.52 (s, 1H), 9.13 (br, 4H, *O*H), 7.05 (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.75 (s, 1H), 6.65 (d, J = 2.1 Hz, 1H), 6.51 (dd, J = 8.0, 2.1 Hz, 1H), 6.40 (d, J = 8.3 Hz, 1H), 6.36 (d, J = 2.3 Hz, 1H), 6.10 (dd, J = 8.3, 2.3 Hz, 1H), 6.05 (d, J = 1.1 Hz, 1H), 3.95 (d, J = 15.6 Hz, 1H), 3.91 (s, 3H), 3.90 (d, J = 15.6 Hz, 1H), 3.75 (s, 3H), 3.64 (s, 3H) ppm.

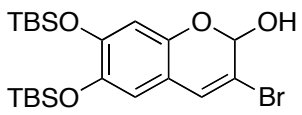
^{13}C NMR (100 MHz, d_6-DMSO): δ 177.4 (**), 157.5, 156.7(**), 156.3, 152.3, 149.3, 148.5, 145.3, 144.9, 143.8, 141.7, 133.8 (*), 129.0, 128.3, 124.4, 124.3, 121.5 (**), 120.5 (*), 118.6, 117.3, 116.8, 115.6, 113.0, 107.0, 106.6 (*), 105.1 (*), 104.0 (*), 101.1 (*), 98.8, 59.5, 55.5, 55.2, 26.6 ppm.

IR (ATR):): $\tilde{\nu}$ = 3166 (m), 2923 (m), 2897 (m), 2362 (w), 2253 (w), 1653 (w), 1551 (m), 1497 (s), 1456 (s), 1344 (s), 1293 (s), 1201 (s), 1023 (s), 999 (s), 823 (s) cm^{-1}.

HRMS (ESI): calc. for $C_{33}H_{27}O_{10}$ $[M+H]^+$: 583.1599,
found: 583.1603.

(*) C obscured, detected by HSQC
(**) C obscured, detected by HMBC

3-bromo-6,7-bis((*tert*-butyldimethylsilyl)oxy)-2*H*-chromen-2-ol (106)



To a stirred solution of protected coumarin **67 (**178 mg, 0.367 mmol, 1 eq.) in CH_2Cl_2 (8 mL) at –78 °C was added DIBAL-H (1 M in toluene, 0.404 ml, 0.404 mmol, 1.1 eq.). The reaction mixture was stirred at –78 °C for 2 h. After completion the reaction the mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with sat. aq. NaCl solution (50 mL) and

dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane: EtOAc 16:1] to provide **106** (170 mg, 95%) as white foam.

R_f: 0.29 (Isohexane:EtOAc 10:1).

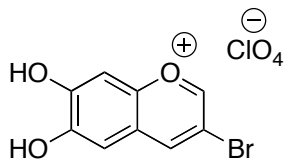
^{1}H NMR (400 MHz, d_3-MeCN): δ 6.95 (s, 1H), 6.69 (s, 1H), 6.48 (s, 1H), 5.82 (d, J = 7.1 Hz, 1H), 5.00 (d, J = 7.1 Hz, 1 *O*H), 0.98 (s, 18H), 0.22 (s, 3H), 0.22 (s, 3H), 0.19 (s, 3H), 0.18 (s, 3H) ppm.

^{13}C NMR (100 MHz, d_3-MeCN): δ 149.0, 145.0, 142.6, 127.7, 118.8, 115.5, 114.3, 110.3, 94.1, 26.4, 26.3, 19.2, 19.1, –3.7, –3.8, –3.8, –3.9 ppm.

IR (ATR): $\tilde{\nu}$ = 3400 (br), 2953 (m), 2928 (m), 2884 (w), 2856 (m), 1612 (w), 1566 (w), 1501 (s), 1471 (m), 1417 (m), 1326 (s), 1252 (s), 1225 (s), 1168 (s), 1140 (s), 1003 (m), 923 (s), 835 (s), 778 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{21}H_{34}O_4BrSi_2^-$ $[M–H]^-$: 485.1184,
found: 485.1178.

3-bromo-6,7-dihydroxychromenylium perchlorate (105)



To a stirred solution of lactol **106** (133 mg, 273 µmol, 1 eq.) in acetic acid (1.5 mL) was added perchloric acid (aq. 70 %, 100 µL, 1.16 mmol, 4.3 eq.) at room temperature. The reaction mixture was stirred for 30 min, while it precipitates. After an additional hour of stirring at room temperature, reaction mixture was transferred in

a falcon tube. The precipitate was collected by sedimentation using a centrifuge. The precipitate was washed with CH_2Cl_2 twice. Product **105** (47 mg, 50 %) was obtained as yellow powder.

R_f: 0.31 (CH_2Cl_2: MeOH 15:1).

mp (CH_2Cl_2): 213.5 °C decomp.

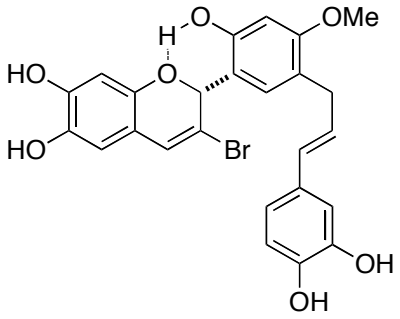
^{1}H NMR (600 MHz, d_3-MeCN): δ 10.19 (br, 1H, *O*H), 9.31 (d, J = 2.1 Hz, 1H), 9.25 (ddd, J = 2.1, 0.8, 0.4 Hz, 1H), 9.05 (br, 1H, *O*H), 7.61 (d, J = 0.8 Hz, 1H), 7.55 (d, J = 0.4 Hz, 1H) ppm.

^{13}C NMR (100 MHz, d_3-MeCN): δ 164.2, 161.5, 158.3, 155.6, 151.7, 126.0, 112.8, 111.0, 104.2 ppm.

IR (ATR): $\tilde{\nu}$ = 3230 (br), 1625 (m), 1501 (s), 1451 (m), 1322 (s), 1304 (s), 1202 (s), 1046 (s), 944 (s), 859 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_9H_6O_3Br^+$ $[M–ClO_4]^+$: 240.9495,
found: 240.9498.

3-bromo-2-(5-(3-(3,4-dihydroxyphenyl)allyl)-2-hydroxy-4-methoxyphenyl)-2*H*-chromene-6,7-diol (107)



To a stirred mixture of bromo flavylium salt **105** (10.0 mg, 29.0 µ mol, 1 eq.) in MeCN (2 mL) was added 2,6-di-*tert*-butyl pyridine (6.30 µL, 29.0 µ mol, 1 eq.) dropwise at 0 °C. After 10 min a solution of benzylstyrene **27** (8.70 mg, 32 µmol, 1.1 eq.) in MeCN was added and upon complete addition, reaction mixture was heated to 50 °C for 2 h. After completion, the reaction mixture was concentrated in vacuo and redissolved in MeOH. The crude product was purified by Sephadex column chromatography (LH-20, MeOH) to afford flavene **107** (9.00 mg, 63 %) as a pale orange wax.

R_f: 0.45 (CH_2Cl_2: MeOH 10:1).

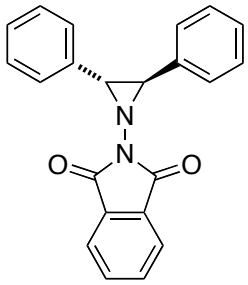
^{1}H NMR (600 MHz, d_6-DMSO): δ 9.71 (s, 1H, *O*H), 9.13 (s, 1H, *O*H), 8.84 (s, 1H, *O*H), 8.79 (s, 1H, *O*H), 8.47 (s, 1H, *O*H), 6.99 (s, 1H), 6.86 (s, 1H), 6.67 (d, J = 1.9 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 6.51 (s, 1H), 6.50 (dd, J = 8.1, 1.9 Hz, 1H), 6.49 (s, 1H), 6.06 (s, 1H), 6.05 (d, J = 15.7 Hz, 1H), 6.03 (s, 1H), 5.87 (dt, J = 15.7, 6.6 Hz, 1H), 3.73 (s, 3H), 3.23 (dd, J = 15.7, 6.6 Hz, 1H), 3.11 (dd, J = 15.7, 6.6 Hz, 1H) ppm.

^{13}C NMR (150 MHz, d_6-DMSO): δ 158.1, 155.1, 146.6, 145.2, 144.7, 143.7, 139.4, 129.8, 129.1, 128.9, 126.7, 125.4, 118.3, 117.5, 115.7, 114.4, 113.5, 112.9, 112.8, 112.7, 103.9, 99.1, 74.0, 55.3, 32.2 ppm.

IR (ATR): $\tilde{\nu}$ = 3399 (w), 3215 (w), 2903 (m), 2375 (w), 2254 (w), 2127 (w), 1537 (m), 1472 (s), 1317 (s), 1261 (s), 1242 (s), 823 (s), 761 (s) cm^{-1}.

HRMS (ESI): calc. for $C_{25}H_{21}BrO_7^-$ $[M–H]^-$: 511.0398,
found: 511.0392.

2,3-diphenylaziridin-1-yl)isoindoline-1,3-dione (179)[41a]



To a stirred solution of *N*-aminophtalimide (1.00 g, 5.55 mmol, 1 eq.) and (*E*)-stilbene (5.00 g, 27.8 mmol, 5 eq.) in CH_2Cl_2 (15 mL) was added $Pb(OAc)_4$ (2.59 g, 5.55 mmol, 1 eq.) in small portions over a period of 10 min at room temperature. The reaction mixture was stirred for 30 min at room temperature. After completion, the reaction mixture was filtered through a pad of celite and washed with CH_2Cl_2 (2 × 3 mL). The combined organic phases were transferred to pentane (80 mL) at 0 °C. After 10 min a precipitate starts forming, which was collected by filtration. The residue was redissolved in CH_2Cl_2 (11 mL) and was stirred with silica (1 g). The organic mixture was filtered through a pad of celite, washed with CH_2Cl_2 (2 × 5 mL) and was concentrated *in vacuo*. Phtalimide **179** (849 mg, 45%) was obtained as a white solid with high purity and was used without further purification in the next step.

R_f: 0.39 (Isohexane:EtOAc 7:3).

mp (CH_2Cl_2): 149.3 – 151.2 °C.

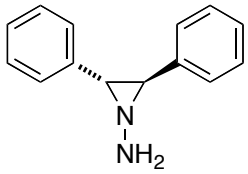
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 – 7.29 (m, 14H), 4.95 (d, J = 5.9 Hz, 1H), 3.97 (d, J = 5.9 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 137.6, 136.8, 134.1, 131.5, 130.3, 129.6, 128.9, 128.9, 128.9, 128.9, 128.8, 128.5, 128.4, 127.8, 127.8, 127.4, 126.7, 123.8, 123.1, 53.8, 46.7 ppm.

IR (ATR): $\tilde{\nu}$ = 3055 (w), 1773 (w), 1709 (s), 1603 (w), 1464 (m), 1452 (m), 1367 (m), 1353 (m), 1308 (m), 1134 (m), 1053 (m), 972 (s), 894 (s), 751 (s), 705 (s), 697 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{22}H_{16}O_2N_2$ $[M^{\bullet}]^+$: 340.1206,
found: 340.1205.

2,3-diphenylaziridin-1-amine (111)[41a]



To a stirred suspension of phtalimide **179** (700 mg, 2.06 mmol, 1 eq.) in EtOH (5.2 mL) was added $N_2H_4 \bullet H_2O$ (5.14 mL, 105 mmol, 51 eq.) at room temperature. The reaction mixture was stirred at 42 °C (rotary evaporator) for 40 min. After completion, the remaining suspension was filtered through a pad of celite. The filtrate was poured in Et_2O/ice (14 mL : 7 g). The organic phase was washed with ice water (3 × 10 mL), dried (K_2CO_3) and filtered through a pad of celite. The filtrate was concentrated to a volume of 10 mL, pentane (15 mL) was added and resulting solution was stored at –25 °C for 10 h upon which colorless needles crystallize. Amino aziridine **111** (302 mg, 71 %) was obtained as colorless needles.

R_f: 0.48 (Isohexane:EtOAc 7:3).

mp (pentane): 103.1 – 105.7 °C.

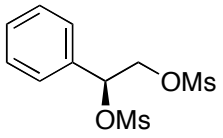
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 – 7.09 (m, 10H), 3.28 (d, J = 4.8 Hz, 1H), 3.14 (d, J = 4.8 Hz, 1H), 3.10 (br s, 2H, NH_2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 139.0, 132.1, 130.7, 128.9, 128.7, 128.7, 128.5, 127.5, 126.7, 126.5, 53.6, 50.0 ppm.

IR (ATR): $\tilde{\nu}$ = 3292 (w), 3223 (w), 3139 (w), 1599 (m), 1494 (m), 1449 (m), 1312 (w), 1097 (m), 1086 (m), 1029 (m), 776 (m), 735 (s), 719 (s), 694 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{14}H_{12}$ $[M^{\bullet}–N_2H_2]^+$: 180.0934,
found: 180.0933.

1-phenylethane-1,2-diyl dimethanesulfonate (180)[41a]



To a stirred solution of styrene glycol (4.31 g, 31.3 mmol, 1 eq.) in pyridine (11.3 mL) was added MsCl (5.46 mL, 70.0 mmol, 2.2 eq.) at 0 °C dropwise over a period of 1 h. Reaction mixture was stirred at this temperature for 4 h. After completion, the reaction mixture was poured in ice (75 g). The resulting mixture was acidified to pH 3 by adding aq. HCl (2 M). The precipitate was collected by filtration and washed with ice water (2 × 13 mL). The precipitate was dissolved in CH_2Cl_2 (25 mL) and was washed with H_2O (3 mL). The organic extract was dried ($MgSO_4$), pentane (35 mL) was added to the remaining solution and was stored at –25 °C. The resulting crystals were washed with pentane (2 × 5 mL), which yielded dimesylate **180** (7.75 g, 84%) as a white solid.

R_f: 0.70 (CH_2Cl_2:MeOH 99:1).

mp (CH_2Cl_2/pentane): 118.3 °C decomp.

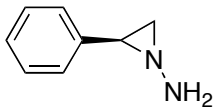
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 – 7.38 (m, 5H), 5.80 (dd, J = 8.6, 3.3 Hz, 1H), 4.53 (dd, J = 11.8, 8.6 Hz, 1H), 4.40 (dd, J = 11.8, 3.3 Hz, 1H), 3.08 (s, 3H), 2.87 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 133.5, 130.4, 129.5, 127.1, 80.9, 70.0, 39.4, 38.4 ppm.

IR (ATR): $\tilde{\nu}$ = 3015 (w), 2934 (w), 1496 (w), 1454 (w), 1413 (w), 1355 (s), 1341 (s), 1179 (s), 1109 (w), 1017 (m), 985 (s), 966 (s), 928 (s), 870 (s), 814 (s), 740 (m), 702 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{10}H_{14}NaO_6S_2$ $[M+Na]^+$: 317.0124,
found: 317.0128.

2-phenylaziridin-1-amine (110)[41a]



To a stirred solution of N_2H_4•H_2O (12.5 mL, 255 mmol, 15 eq.) was added dimesylate **180** (5.00 g, 17.0 mmol, 1 eq.) at room temperature. Pentane (150 mL) was added and was stirred for 24 h at room temperature. The reaction mixture was extracted with pentane (2 × 10 mL). Concentration *in vacuo* afforded amino aziridine **110** (1.85 g, 81 %) as a white solid.

R_f: 0.28 (Isohexane:EtOAc 7:3).

mp (pentane): 18 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 – 7.15 (m, 5H), 3.59 (br s, 2H, NH_2), 2.61 (dd, J = 7.8, 4.7 Hz, 1H), 2.04 (dd, J = 4.7, 0.6 Hz, 1H), 2.01 (dd, J = 7.8, 0.6 Hz, 1H) ppm.

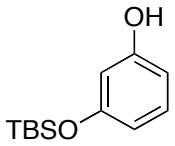
^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 128.5, 127.2, 126.3, 45.7, 41.7 ppm.

IR (ATR): $\tilde{\nu}$ = 3309 (w), 3247 (w), 3159 (w), 3061 (w), 2985 (w), 1604 (m), 1494 (m), 1455 (m), 1377 (w), 1087 (m), 1066 (m), 915 (m), 731 (s), 695 (s) cm^{-1}.

HRMS (EI):	calcd. for C_8H_8 $[M^{\square}–N_2H_2]^+$:	104.0621,
	found:	104.0613.

V. 5. Experimental towards santalin A and B

3-((*tert*-butyldimethylsilyl)oxy)phenol (123)[28]



To a stirred mixture of resorcinol **86** (5.00 g, 45.4 mmol, 1 eq.) in DMF (15 mL) was added TBSCl (9.55 g, 47.7 mmol, 1.05 eq.) and imidazole (6.50 g, 95.5 mmol, 2.1 eq.) at 0 °C. After 2 h stirring at this temperature, the reaction mixture was allowed to warm to room temperature and was stirred for an additional 2 h. After completion, H_2O (30 mL) was added to the reaction mixture and the biphasic mixture was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with aq. NaCl (10%, 2 × 30 mL), sat. aq. NaCl (50 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography [Isohexane:EtOAc 16:1 → 10:1) to afford TBS resorcinol **123** (4.58 g, 45%) as a pale yellow oil.

R_f: 0.42 (Isohexane: EtOAc 7:1).

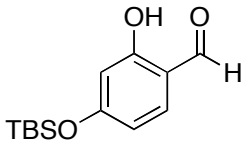
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (t, J = 8.1 Hz, 1H), 6.44 – 6.41 (m, 2H), 6.35 (t, J = 2.3 Hz, 1H), 4.68 (s, 1H, *O*H), 0.98 (s, 9H), 0.19 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 156.7, 130.1, 112.9, 108.6, 107.7, 25.9, 18.4, –4.2 ppm.

IR (ATR): $\tilde{\nu}$ = 3340 (m), 2956 (w), 2930 (w), 1591 (m), 1472 (m), 1143 (s), 979 (s), 835 (s), 780 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{12}H_{20}O_2Si^+$ $[M^\bullet]^+$: 224.1227,
found: 224.1215.

4-((*tert*-butyldimethylsilyl)oxy)-2-hydroxybenzaldehyde (124)[28]



To a stirred solution of TBS resorcinol **123** (4.00 g, 17.9 mmol, 1 eq.) in THF (150 mL) was added successively anhydrous $MgCl_2$ (3.39 g, 35.7 mmol, 2 eq.), NEt_3 (5.00 mL, 35.7 mmol, 2 eq.) and $(CH_2O)_n$ (1.61 g, 53.6 mmol, 3 eq.) and the resulting suspension was heated to 70 °C for 2 h 30 min. After completion, the reaction mixture was cooled to room temperature and Et_2O (200 mL) was added. After washing with aq. HCl (1 M, 2 × 70 mL), H_2O (2 × 70 mL) and sat. aq. NaCl (100 mL), the organic phase was dried ($MgSO_4$). The crude product was purified by flash column chromatography [Isohexane:EtOAc 7:1] to afford benzaldehyde **124** (3.92 g, 87%) as a colorless oil.

R_f: 0.52 (Isohexane: EtOAc 10:1).

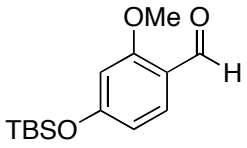
^{1}H NMR (400 MHz, $CDCl_3$): δ 11.33 (s, 1H, *O*H), 9.73 (d, J = 0.5 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 6.47 (dd, J = 8.5, 2.2 Hz, 1H), 6.39 (d, J = 2.2 Hz, 1H), 0.98 (s, 9 H), 0.26 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.8, 164.3, 164.0, 135.7, 116.0, 113.3, 107.9, 25.7, 18.5, –4.1 ppm.

IR (ATR): $\tilde{\nu}$ = 3055 (w), 2931 (m), 2744 (w), 1646 (s), 1623 (s), 1218 (s), 804 (s), 780 (s), 704 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{13}H_{20}O_3Si^+$ $[M^\bullet]^+$: 252.1176,
found: 252.1175.

4-((*tert*-butyldimethylsilyl)oxy)-2-methoxybenzaldehyde (125)[59]



To a stirred solution of benzaldehyde **124** (2.82 g, 11.2 mmol, 1 eq.) in Et_2O (45 mL) was added successively MeI (3.50 mL, 56.0 mmol, 5 eq.) and Ag_2O (10.4 g, 44.8 mmol, 4.0 eq.) at room temperature. Reaction mixture was stirred for 10 h. After completion, the solids were removed by filtration through a plug of celite and washed with Et_2O (20 mL). The filtrate was washed with sat. aq. NH_4Cl (60 mL) and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with sat. aq. NaCl (30 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography [Isohexane:EtOAc 30:1] to afford benzaldehyde **125** (2.41 g, 81%) as a colorless solid.

R_f: 0.48 (Isohexane:EtOAc 7:1).

mp (EtOAc): 54.9 – 57.6 °C.

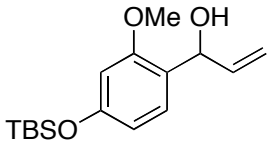
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.29 (d, J = 0.8 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 6.47 (ddd, J = 8.5, 2.1, 0.8 Hz, 1H), 6.39 (d, J = 2.1 Hz, 1H), 3.88 (s, 3H), 0.99 (s, 9H), 0.25 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 163.8, 163.2, 130.6, 119.6, 112.7, 103.5, 55.8, 25.8, 18.5, –4.1 ppm.

IR (ATR): $\tilde{\nu}$ = 2923 (w), 2856 (w), 1673 (m), 1594 (m), 1206 (s), 1165 (s), 833 (s), 776 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{14}H_{22}O_3Si^+$ $[M]^+$: 266.1333,
found: 266.1330.

1-(4-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)prop-2-en-1-ol (126)



To a stirred solution of benzaldehyde **125** (3.00 g, 11.3 mmol, 1 eq.) in THF (25 mL) was added vinylmagnesiumbromide (1 M solution in THF, 13.6 mL, 13.6 mmol, 1.2 eq.) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C. Upon completion, aq. sat. NH_4Cl (15 mL) was added and extracted with Et_2O (3 x 30 mL). The organic phases were combined and washed with aq. sat. NaCl (30 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane: EtOAc 12:1] to afford allylic alcohol **126** (2.19 g, 66 %) as a colorless oil.

R_f: 0.23 (Isohexane: EtOAc 7:1).

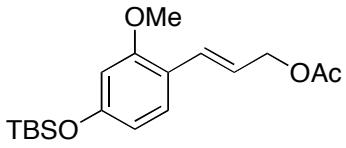
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (d, J = 8.0 Hz, 1H), 6.44 – 6.39 (m, 2H), 6.12 (ddd, J = 17.2, 10.4, 5.5 Hz, 1H), 5.38 – 5.25 (m, 2H), 5.15 (dt, J = 10.4, 1.6 Hz, 1H), 3.81 (s, 3H), 2.67 (d, J = 5.9 Hz, 1H), 0.99 (s, 9H), 0.21 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0, 156.6, 139.9, 128.2, 124.0, 114.5, 112.0, 103.9, 71.3, 55.6, 25.9, 18.4, –4.2, –4.2 ppm.

IR (ATR): $\tilde{\nu}$ = 3355 (br), 2954 (m), 2928 (m), 2856 (m), 1740 (w), 1603 (w), 1509 (s), 1463 (m), 1279 (s), 1249 (s), 1229 (s), 1153 (s), 1037 (s), 915 (s), 837 (s), 821 (s), 779 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{16}H_{25}O_2Si^+$ $[M–OH]^+$: 277.1618,
found: 277.1622.

1-(4-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)allyl acetate (130)



To a solution of allylic alcohol **126** (200 mg, 0.680 mmol, 1 eq.) in CH_2Cl_2 (3 mL) was added acetic anhydride (100 µL, 1.02 mmol, 1.5 eq.), pyridine (110 µL, 1.36 mmol, 2 eq.) and 4-dimethlyaminopyridine (2.00 mg, 6.80 µmol, 1 mol-%) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. After completion, H_2O (5 mL) was added to reaction mixture and was extracted with Et_2O (3 × 10 mL). The organic extracts were washed with sat. aq. NaCl (4 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 7:1] to afford acetoxy allyl phenol **130** (119 mg, 52 %) as a colorless oil.

R_f: 0.39 (Isohexane:EtOAc 10:1).

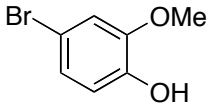
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, J = 9.0 Hz, 1H), 6.88 (d, J = 16.0 Hz, 1H), 6.41 (dd, J = 8.3, 2.3 Hz, 1H), 6.36 (d, J = 2.2 Hz, 1H), 6.21 (dt, J = 16.0, 6.7 Hz, 1H), 4.70 (dd, J = 6.7, 1.1 Hz, 2H), 3.81 (s, 3H), 2.08 (s, 3H), 0.99 (s, 9H), 0.21 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 158.2, 157.2, 129.7, 128.1, 121.7, 118.9, 112.3, 103.8, 66.2, 55.6, 25.9, 21.3, 18.5, –4.1 ppm.

IR (ATR): $\tilde{\nu}$ = 3415 (w), 2955 (m), 2929 (m), 2857 (m), 1739 (s), 1603 (s), 1574 (m), 1500 (s), 1450 (m), 1289 (s), 1228 (s), 1201 (s), 1162 (s), 1034 (m), 976 (s), 836 (s), 778 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{16}H_{25}O_2Si^+$ $[M–OAc]^+$: 277.1618,
found: 277.1622.

4-bromo-2-methoxyphenol (135)[60]



To a stirred solution of guaiacol **134** (4.97 g, 40.0 mmol, 1 eq.) in DMF (35 mL) was added *N*-bromosuccinimide (7.14 g, 40.1 mmol, 1 eq.) in small portions at 0 °C. The reaction mixture was stirred for 1 h at this temperature. After completion, sat. aq. $Na_2S_2O_3$ (20 mL) was added to reaction mixture and the resulting biphasic mixture was extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with aq. NaCl (10%, 2 × 50 mL), sat. aq. NaCl (30 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 10:1] to afford bromoguaiacol **135** (5.14 g, 63%) as a pale brown oil.

R_f: 0.26 (Isohexane:EtOAc 7:1).

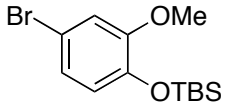
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01 – 6.96 (m, 2H), 6.79 (dd, J = 8.0, 0.6 Hz, 1H), 5.55 (s, 1H, *O*H), 3.88 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 145.1, 124.4, 116.0, 114.4, 111.8, 56.4 ppm.

IR (ATR): $\tilde{\nu}$ = 3476 (m), 3393 (m), 2972 (w), 2929 (w), 2840 (w), 1590 (m), 1492 (s), 1453 (m), 1433 (m), 1331 (s), 1287 (s), 1256 (s), 1221 (s), 1173 (s), 1124 (s), 1023 (s), 855 (s), 797 (s), 759 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_7H_7O_2Br^+$ $[M^\bullet]^+$: 201.9624,
found: 201.9621

(4-bromo-2-methoxyphenoxy)(*tert*-butyl)dimethylsilane (136)[61]



To a stirred solution of bromo guaiacol **135** (5.14 g, 25.3 mmol, 1 eq.) in DMF (20 mL) was added TBSCl (4.58 g, 30.4 mmol, 1.2 eq.), imidazole (4.13 g, 30.4 mmol, 2.4 eq.) and 4-dimethylaminopyridine (309 mg, 2.53 mmol, 10 mol-%) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 6 h. After completion, H_2O (30 mL) was added and the biphasic mixture was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with aq. NaCl (10%, 2 × 15 mL), sat. aq. NaCl (20 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane] to afford TBS phenol **136** (6.72 g, 84%) as colorless oil.

R_f: 0.58 (Isohexane:EtOAc 10:1).

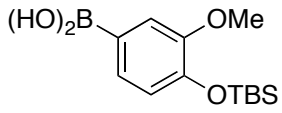
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 – 6.91 (m, 2H), 6.71 (d, J = 8.1 Hz, 1H), 3.79 (s, 3H), 0.98 (s, 9H), 0.14 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 152.0, 144.6, 123.9, 122.3, 115.7, 113.6, 55.9, 25.9, 18.7, –4.5 ppm.

IR (ATR): $\tilde{\nu}$ = 2953 (m), 2928 (m), 2855 (m), 1585 (m), 1494 (s), 1471 (m), 1444 (m), 1397 (m), 1297 (m), 1266 (s), 1254 (s), 1222 (s), 1178 (s), 908 (s), 832 (s), 779 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{13}H_{21}BrO_2Si^+$ $[M^\bullet]^+$: 316.0489,
found: 316.0468.

(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenyl)boronic acid (137)



To a stirred solution of bromide **136** (200 mg, 0.630 mmol, 1 eq.) in toluene/THF (1:1, 2 mL) was added B(O*i*Pr)$_3$ (175 µl, 0.756 mmol, 1.2 eq.) at –78 °C. After 5 min, *n*-BuLi (2.5 M in THF, 302 µL, 0.756 mmol, 1.2 eq.) was added dropwise at -78 °C. The reaction mixture was stirred for 1 h 30 min at this temperature. After completion, aq. HCl (2 M, 3 mL) was added and the reaction mixture was warmed to room temperature. After 1 h, the biphasic mixture was extracted with Et_2O (3 × 20 mL), washed with sat. aq. NaCl (3 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 5:3] to afford boronic acid **137** (91.0 mg, 51%) as a white wax.

R_f: 0.20 (Isohexane:EtOAc 7:3).

^{1}H NMR (400 MHz, D_2O/d_6-acetone): δ 7.43 (d, J = 1.5 Hz, 1H), 7.34 (dd, J = 7.8, 1.5 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 3.78 (s, 3H), 0.94 (s, 9H), 0.11 (s, 6H) ppm.

^{13}C NMR (100 MHz, D_2O/d_6-acetone): δ 150.2, 147.0, 127.6, 120.0, 117.8, 54.8, 25.2, 18.1, –5.3 ppm.

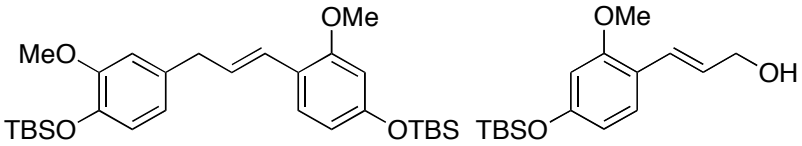
(C-B is obscured)

IR (ATR): $\tilde{\nu}$ = 3218 (br), 2955 (m), 2928 (m), 2856 (m), 1596 (m), 1510 (m), 1463 (m), 1449 (m), 1405 (s), 1333 (s), 1311 (s), 1271 (s), 1215 (s), 1177 (s), 1124 (s), 1037 (m), 924 (s), 876 (s), 836 (s), 780 (s), 713 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{13}H_{22}BO_4Si^-[M–H]^-$: 281.1386,
found: 281.1372.

(*E*)-*tert*-butyl(4-(3-(4-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)allyl)-2-methoxyphenoxy)dimethylsilane (138)

(*E*)-3-(4-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)prop-2-en-1-ol (140)



To a mixture of allylic alcohol **126** (442 mg, 1.5 mmol, 1 eq.) and boronic acid **137** (444 mg, 1.57 mmol, 1.05 eq.) in CH_2Cl_2 (15 mL) was added $Pd(PPh_3)_4$ (104 mg, 0.09 mmol, 6 mol-%) in a pressure tube. The reaction mixture was heated to 80 °C for 10 h. After completion, sat. aq. NH_4Cl (5 mL) was added and the biphasic mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with sat. aq. NaCl (15 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 50:1] to afford benzylstyrene **138** (215 mg, 28 %) and allyl alcohol **140** (260 mg, 59 %) as a pale yellow oil.

(*E*)-*tert*-butyl(4-(3-(4-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)allyl)-2-methoxyphenoxy)dimethylsilane (138)

R_f: 0.38 (Isohexane:EtOAc 10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, J = 8.3 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 2.1 Hz, 1H), 6.70 (dd, J = 2.1, 0.7 Hz, 1H), 6.67 (dd, J = 8.0, 0.5 Hz, 1H), 6.40 (dd, J = 8.2, 2.3 Hz, 1H), 6.37 (d, J = 2.3, 1H), 6.22 (dt, J = 15.8, 7.0 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.47 (dd, J = 7.0, 0.7 Hz, 2H), 1.00 (s, 9H), 0.99 (s, 9H), 0.20 (s, 6H), 0.15 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 156.2, 151.0, 143.4, 134.4, 128.4, 127.3, 125.3, 120.9, 120.9, 120.3, 113.0, 112.2, 103.8, 55.7, 55.6, 39.7, 26.0, 25.9, 18.7, 18.5, –4.1, –4.4 ppm.

IR (ATR): $\tilde{\nu}$ = 2954 (m), 2929 (m), 2895 (w), 2857 (m), 1603 (m), 1510 (s), 1500 (s), 1284 (s), 1252 (s), 1201 (s), 1162 (s), 1037 (s), 978 (s), 835 (s), 777 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{29}H_{45}O_4Si_2^+$ $[M–H]^+$: 513.2862,
found: 513.2856.

(*E*)-3-(4-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)prop-2-en-1-ol (140)

R_f: 0.24 (Isohexane:EtOAc 4:1).

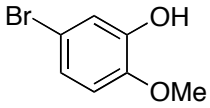
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, J = 8.3 Hz, 1H), 6.84 (d, J = 16.1 Hz, 1H), 6.42 (dd, J = 8.3, 2.3 Hz, 1H), 6.37 (d, J = 2.3 Hz, 1H), 6.29 (dt, J = 16.1, 6.1 Hz, 1H), 4.30 (dd, J = 6.1, 1.1 Hz, 2H), 3.81 (s, 3H), 0.99 (s, 9H), 0.22 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0, 156.9, 127.8, 127.3, 126.6, 119.3, 112.3, 103.8, 64.8, 55.6, 25.9, 18.5, –4.1 ppm.

IR (ATR): $\tilde{\nu}$ = 3338 (br), 2953 (m), 2929 (m), 2857 (m), 2360 (w), 1603 (s), 1574 (w), 1500 (s), 1463 (m), 1450 (w), 1413 (w), 1290 (s), 1256 (m), 1202 (s), 1163 (s), 978 (s), 863 (s), 838 (s), 779 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{16}H_{25}O_2Si$ $[M–OH]^+$: 277.1618,
found: 277.1623

5-bromo-2-methoxyphenol (142)[62]



To a stirred solution of acetoxy guaiacol (**141**) (4.00 g, 24.0 mmol, 1 eq.) in MeCN (60 mL) was added *N*-bromo-succinimide (4.71 g, 26.5 mmol, 1.1 eq.) and the resulting reaction mixture was heated at 60 °C for 4 h. After completion, the reaction mixture was cooled to room temperature, H_2O (100 mL) was added and the resulting mixture was extracted with EtOAc (3 × 100 mL). The organic extracts were washed successively with H_2O (100 mL), sat. aq. Na_2SO_3 (70 mL), H_2O (100 mL), sat. aq. NaCl (70 mL) and dried (Na_2SO_4).

The crude product was redissolved in MeOH (150 mL) and KOH (2.80 g, 50 mmol, 2.1 eq.) dissolved in MeOH (20 mL) was added. The reaction mixture was heated at 70 °C for 6 h. After completion, reaction mixture was cooled to room temperature and aq. HCl (6 M, 40 mL) was added carefully. The resulting mixture was extracted with CH_2Cl_2 (2 × 100 mL) and the organic phases were washed with H_2O (70 mL), sat. aq. NaCl (70 mL) and were dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 4:1] to afford bromo guaiacol **142** (4.20 g, 87%) as white crystals.

R_f: 0.41 (Isohexane:EtOAc 10:1).

mp (EtOAc): 64.9 – 67.2°C.

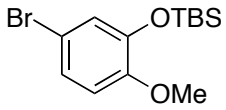
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07 (d, J = 2.4 Hz, 1H), 6.96 (dd, J = 8.6, 2.4 Hz, 1H), 6.71 (d, J = 8.6 Hz, 1H), 5.65 (s, 1H, *O*H), 3.87 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 146.7, 146.1, 123.0, 118.0, 113.5, 112.1, 56.3 ppm.

IR (ATR): $\tilde{\nu}$ = 3476 (m), 3393 (br), 2972 (w), 2839 (w), 1590 (m), 1492 (s), 1453 (m), 1432 (m), 1331 (m), 1288 (m), 1257 (s), 1222 (s), 1173 (s), 1023 (s), 855 (s), 797 (s) cm^{-1}.

HRMS (EI):	calcd. for $C_7H_7O_2Br^+$ $[M^•]^+$:	201.9624,
	found:	201.9620.

(5-bromo-2-methoxyphenoxy)(*tert*-butyl)dimethylsilane (143)[63]



To a stirred solution of bromo guaiacol **142** (3.40 g, 16.8 mmol, 1 eq.) in DMF (30 mL) was added TBSCl (3.70 g, 24.5 mmol, 1.5 eq.), imidazole (2.90 g, 42.5 mmol, 2.5 eq.) and 4-dimethylaminopyridine (204 mg, 1.68 mmol, 10 mol-%) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 4 h. After completion, H_2O (50 mL) was added and the biphasic mixture was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with aq. NaCl (10%, 2 × 30 mL), sat. aq. NaCl (30 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane] to afford TBS phenol **143** (4.30 g, 81%) as colorless oil.

R_f: 0.75 (Isohexane:EtOAc 10:1).

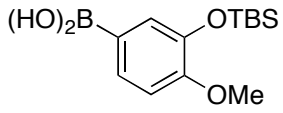
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (dd, J = 8.5, 2.4 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 3.78 (s, 3H), 0.99 (s, 9H), 0.16 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 150.7, 146.2, 124.6, 124.3, 113.5, 112.6, 55.8, 25.9, 18.7, –4.5 ppm.

IR (ATR): $\tilde{\nu}$ = 2954 (m), 2928 (m), 2894 (w), 2855 (m), 1586 (m), 1495 (s), 1444 (m), 1397 (m), 1297 (m), 1266 (s), 1254 (s), 1222 (s), 1120 (s), 1037 (m), 908 (s), 832 (s), 779 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{13}H_{21}BrO_2Si^+$ $[M^\bullet]^+$: 316.0475,
found: 316.0468.

(3-((*tert*-butyldimethylsilyl)oxy)-4-methoxyphenyl)boronic acid (144)[64]



To a stirred solution of bromide **143** (317 mg, 1.00 mmol, 1 eq.) in THF (3 mL) was added *n*-BuLi (2.5 M in THF, 480 µL, 1.20 mmol, 1.2 eq.) dropwise at –78 °C. After 30 min, B(O*i*-Pr)$_3$ (283 µL, 1.20 mmol, 1.2 eq.) was added and was stirred at –78 °C for 1 h 30 min. The reaction mixture was warmed to room temperature and aq. HCl (2 M, 4 mL) was added. After 20 min, the biphasic mixture was extracted with Et_2O (3 × 25 mL), washed with sat. aq. NaCl (3 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 5:3] to afford boronic acid **144** (104 mg, 37%) as a white wax.

R_f: 0.36 (Isohexane:EtOAc 7:3).

^{1}H NMR (400 MHz, D_2O/d_6-acetone): δ 7.45 (dd, J = 8.3, 1.8 Hz, 1H), 7.36 (d, J = 1.8 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 3.80 (s, 3H), 0.97 (s, 9H), 0.11 (s, 6H) ppm.

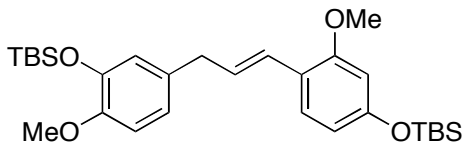
^{13}C NMR (100 MHz, D_2O/d_6-acetone): δ 153.8, 144.9, 129.5, 127.2, 112.1, 55.6, 26.1, 19.0, –4.5 ppm.

(C-B is obscured)

IR (ATR): $\tilde{\nu}$ = 3210 (br), 2953 (m), 2928 (m), 2894 (w), 2856 (s), 1596 (m), 1503 (s), 1470 (s), 1454 (s), 1406 (m), 1264 (s), 1223 (s), 1193 (s), 1113 (m), 1032 (m), 903 (s), 836 (s), 779 (s) cm^{-1}.

HRMS (ESI): calc. for $C_{13}H_{22}BO_4Si^-$ $[M–H]^-$: 281.1386,
found: 281.1376.

(*E*)-*tert*-butyl(5-(3-(4-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)allyl)-2-methoxyphenoxy)dimethylsilane (145)



To a mixture of allylic alcohol **126** (155 mg, 0.510 mmol, 1 eq.) and boronic acid **144** (156 mg, 0.550 mmol, 1.05 eq.) in CH_2Cl_2 (12 mL) was added $Pd(PPh_3)_4$ (35.0 mg, 40.0 µmol, 6 mol-%) in a pressure tube. The reaction mixture was heated to 80 °C for 9 h. After completion, sat. aq. NH_4Cl (7 mL) was added and the biphasic mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with sat. aq. NaCl (10 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 50:1] to afford benzylstyrene **145** (110 mg, 41 %) as a pale yellow oil.

R_f: 0.42 (Isohexane:EtOAc 10:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24 (d, J = 8.3 Hz, 1H), 6.80 – 6.72 (m, 3H), 6.65 (d, J = 15.9 Hz, 1H), 6.38 (dd, J = 8.3, 2.3 Hz, 1H), 6.35 (d, J = 2.3 Hz, 1H), 6.19 (dt, J = 15.9, 7.0 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.42 (dd, J = 7.0, 1.3 Hz, 2H), 0.99 (s,

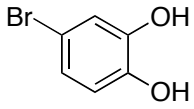
9H), 0.98 (s, 9H), 0.20 (s, 6H), 0.15 (s, 6H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 157.5, 156.2, 149.5, 145.1, 133.7, 128.5, 127.3, 125.3, 121.7, 121.7, 120.4, 112.5, 112.2, 103.8, 55.9, 55.6, 39.2, 26.0, 25.9, 18.7, 18.5, –4.1, –4.4 ppm.

IR (ATR): $\tilde{\nu}$ = 2952 (m), 2945 (m), 2861 (m), 1597 (s), 1574 (s), 1510 (s), 1475 (s), 1450 (s), 1414 (m), 1276 (s), 1259 (s), 1162 (s), 983 (s), 850 (s), 790 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{29}H_{45}O_4Si_2^+$ $[M–H]^+$: 513.2862,
found: 513.2856.

4-bromobenzene-1,2-diol (147)[65]



To a stirred solution of catechol (**146**) (2.30 g, 20.0 mmol, 1 eq.) in MeCN (15 mL) was added HBF_4•Et_2O (5.10 mL, 20.0 mmol, 1 eq.) at –20 °C. After 5 min, *N*-bromo-succinimide (3.70 g, 21.0 mmol, 1.05 eq.) was added in small portions over a period of 10 min. After 30 min, reaction was warmed to room temperature and was stirred at this temperature for 10 h. After completion, H_2O (50 mL) was added to reaction mixture and was extracted with Et_2O (3 × 70 mL). The organic extracts were washed with aq. $NaHSO_3$ (4% w/v, 2 × 50 mL), sat. aq. NaCl (50 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 4:1] to afford bromocatechol **147** (2.37 g, 63%) as a colorless solid.

R_f: 0.19 (Isohexane:EtOAc 10:1).

mp (EtOAc): 86.7 – 88.3 °C.

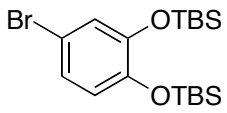
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (d, J = 2.3 Hz, 1H), 6.93 (dd, J = 8.5, 2.3 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H), 5.45 (s, 1H, *O*H), 5.32 (s, 1H, *O*H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 142.9, 124.2, 118.9, 116.9, 112.8 ppm.

IR (ATR): $\tilde{\nu}$ = 3337 (br), 1596 (m), 1499 (s), 1425 (s), 1350 (m), 1324 (m), 1264 (s), 1234 (s), 1175 (s), 1104 (s), 1068 (m), 881 (s), 847 (m), 797 (s), 775 (s) cm^{-1}.

HRMS (EI):	calcd. for $C_6H_5O_2Br^+$ $[M^\bullet]^+$:	187.9467,
	found:	187.9463

((4-bromo-1,2-phenylene)bis(oxy))bis(*tert*-butyldimethylsilane) (148)[66]



To a stirred solution of bromo catechol **147** (1.08 g, 5.70 mmol, 1 eq.) in DMF (20 mL) was added TBSCl (1.72 g, 11.4 mmol, 2.4 eq.), imidazole (1.86 g, 4.80 mmol, 4.8 eq.) and 4-dimethylaminopyridine (139 mg, 0.200 mmol, 20 mol-%) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 10 h. After completion, H_2O (30 mL) was added and the biphasic mixture was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with aq. NaCl (10%, 20 mL), sat. aq. NaCl (30 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane] to afford TBS phenol **148** (2.44 g, 99%) as colorless solid.

R_f: 0.87 (Isohexane:EtOAc 30:1).

mp (Isohexane): 41.6 – 45.7 °C.

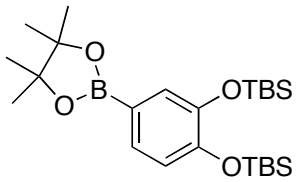
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (d, J = 2.3 Hz, 1H), 6.92 (dd, J = 8.4, 2.3 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 0.98 (s, 9H), 0.97 (s, 9H), 0.20 (s, 6H), 0.18 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 148.1, 146.6, 124.5, 124.4, 122.4, 112.9, 26.1, 26.1, 18.7, 18.7, –3.9, –3.9 ppm.

IR (ATR): $\tilde{\nu}$ = 2953 (m), 2928 (m), 2857 (m), 1581 (m), 1491 (s), 1471 (s), 1396 (m), 1287 (s), 1252 (s), 1210 (s), 1119 (s), 935 (s), 894 (s), 836 (s), 777 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{18}H_{33}BrO_2Si_2^+$ $[M^{\bullet}]^+$: 416.1197,
found: 416.1189.

((4-(3,3,4,4-tetramethylborolan-1-yl)-1,2-phenylene)bis(oxy))bis(*tert*-butyldimethylsilane) (150)[67]



To a stirred solution of bromide **148** (84.0 mg, 0.200 mmol, 1 eq.) in THF (2 mL) was added *n*-BuLi (2.5 M in THF, 96.0 µL, 0.240 mmol, 1.2 eq.) dropwise at –78 °C. After 40 min, B(O*i*Pr)(pinacol) (49.0 µL, 0.240 mmol, 1.2 eq.) was added and was stirred at –78 °C for 2 h. After completion, H_2O (5 mL) was added and the biphasic mixture was extracted with Et_2O (3 × 15 mL), washed with sat. aq. NaCl (10 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography

[Isohexane:EtOAc 40:1] to afford boronic acid **150** (80.0 mg, 86%) as a white powder.

R_f: 0.81 (Isohexane:EtOAc 30:1).

mp (EtOAc): 51.2 – 53.7°C.

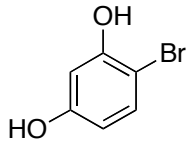
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (dd, J = 7.9, 1.6 Hz, 1H), 7.25 (d, J = 1.6 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 1.32 (s, 12H), 1.00 (s, 9H), 0.98 (s, 9H), 0.20 (s, 6H), 0.20 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 146.6, 128.8, 127.7, 120.9, 83.7, 26.2, 26.2, 25.1, 18.8, 18.6, –3.8, –3.9 ppm.

IR (ATR): $\tilde{\nu}$ = 2956 (m), 2928 (m), 2857 (m), 1597 (m), 1511 (m), 1402 (s), 1351 (s), 1283 (s), 1251 (s), 1211 (s), 1144 (s), 1124 (s), 970 (s), 953 (s), 897 (s), 833 (s), 779 (s) cm^{-1}.

HRMS (EI): calc. for $C_{24}H_{45}BO_4Si_2^+$ $[M^\bullet]^+$: 464.2944,
found: 464.2946.

4-bromobenzene-1,3-diol (154)[68]



A stirred mixture of 2,4-dihydroxybenzoic acid (**153**) (10.0 g, 64.9 mmol, 1 eq.) and acetic acid (75 mL) was heated to 50 °C. After cooling to 35 °C a solution of bromine

(3.30 mL, 10.4 g, 64.9 mmol, 1 eq.) in acetic acid (55 mL) was added dropwise over a period of 1 h 30 min. The mixture was poured in H_2O (1 L) and kept over night at 0 °C. The precipitate was collected, washed with ice cold H_2O (100 mL) and air dried over night. Afterwards the solid was suspended in H_2O (325 mL), heated to reflux for 1 h, hot filtrated and cooled in an ice bath for 1 h. The precipitate was collected and washed with ice cold H_2O (20 mL). Then the precipitate was again suspended in H_2O (175 mL), refluxed for 29 h, filtered and cooled to room temperature. After addition of sat. aq. NaCl (10 mL) the resulting solution was extracted with Et_2O (2 × 100 mL), the combined organic phases washed with sat. aq. NaCl (50 mL) and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded **154** (6.48 g, 53%) as a colorless solid.

R_f: 0.34 (Isohexane: EtOAc 7:3).

mp (acetone): 100.2 – 101.8 °C.

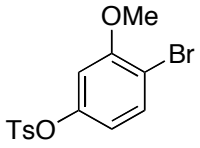
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, J = 8.7 Hz, 1H), 6.54 (d, J = 2.9 Hz, 1 H), 6.34 (dd, J = 8.7, 2.9 Hz, 1H), 5.47 (s, 1H, *O*H), 4.84 (s, 1H, *O*H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 153.2, 132.4, 109.6, 103.6, 101.3 ppm.

IR (ATR): $\tilde{\nu}$ = 3462 (m), 3317 (m), 1619 (m), 1505 (s), 1157 (s), 1119 (s), 966 (s), 834 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_6H_4BrO_2^-$ $[M–H]^-$: 186.9400,
found 186.9401.

4-bromo-3-methoxyphenyl 4-methylbenzenesulfonate (155)[68]



To a stirred solution of 3-bromobenzene-1,2-diol **154** (1.00 g, 5.29 mmol, 1 eq.) in acetone (75 mL) was added tosyl chloride (1.11 g, 5.82 mmol, 1.1 eq.) and K_2CO_3 (2.20 g, 15.9 mmol, 1.5 eq.). After heating at 80 °C for 24 h MeI (0.660 mL, 11.0 mmol, 2.1 eq.) was added and heating continued for 3 h 30 min. The mixture was cooled to room temperature, the solids removed by filtration and washed with acetone (50 mL). Then the filtrate was concentrated *in vacuo* to 25 mL volume. After addition of H_2O (50 mL) and sat. aq. NaCl (20 mL) the solution was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with H_2O (20 mL), sat. aq. NaCl (5 mL) and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded **155** (1.85 g, 98%) as a colorless solid.

R_f: 0.45 (Isohexane: EtOAc 4:1).

mp (acetone): 68.2 – 70.6 °C.

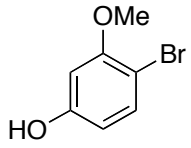
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 – 7.70 (m, 2H), 7.40 (d, J = 8.6 Hz, 1H), 7.35 – 7.31 (m, 2H), 6.60 (d, J = 2.6 Hz, 1H), 6.41 (dd, J = 8.6, 2.6 Hz, 1H), 3.78 (s, 3H), 2.45 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 149.7, 145.8, 133.5, 132.3, 130.0, 128.8, 115.4, 110.1, 107.2, 56.5, 21.9 ppm.

IR (ATR): $\tilde{\nu}$ = 2939 (w), 1594 (m), 1177 (s), 1136 (s), 946 (s), 783 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{14}H_{13}BrO_4S^+$ $[M^{\bullet}]^+$: 355.9718,
found: 355.9715.

4-bromo-3-methoxyphenol (156)[68]



To a stirred solution of 4-bromo-3-methoxyphenyl 4-methylbenzenesulfonate **155** (1.71 g, 4.79 mmol, 1 eq.) in MeOH (60 mL) was added aq. NaOH (2 M, 11.0 mL, 880 mg, 22.0 mmol, 4.6 eq.). The mixture was heated to 60 °C for 3 h. Then the mixture was concentrated *in vacuo* and the residue was neutralized under ice bath cooling with aq. HCl (2 M). After addition of sat. aq. NaCl (10 mL) the mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phases were washed with H_2O (40 mL), sat. aq. NaCl (50 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the crude product purified by flash column chromatography [Isohexane: EtOAc 7:1] to provide **156** (831 mg, 85%) as a colorless solid.

R_f: 0.51 (Isohexane: EtOAc 7:3).

mp (EtOAc): 71.1 – 73.4 °C.

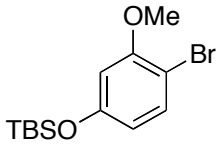
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, J = 8.5 Hz, 1H), 6.45 (d, J = 2.7 Hz, 1H), 6.33 (dd, J = 8.5, 2.7 Hz, 1H), 4.97 (s, 1H, *O*H), 3.85 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 156.3, 133.5, 108.7, 102.4, 100.6, 56.3 ppm.

IR (ATR): $\tilde{\nu}$ = 3454 (m), 1582 (m), 1296 (s), 1042 (s), 821 (s), 791 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_7H_6BrO_2^-$ $[M–H]^-$: 200.9557,
found: 200.9558.

(4-bromo-3-methoxyphenoxy)(*tert*-butyl)dimethylsilane (157)[49]



To a stirred solution of 4-bromo-3-methoxyphenol (**156**) (379 mg, 1.87 mmol, 1 eq.) in DMF (5 mL) was added successively imidazole (166 mg, 2.44 mmol, 1.3 eq.), 4-dimethylaminopyridine (18 mg, 0.15 mmol, 8 mol-%) and TBSCl (489 mg, 2.44 mmol, 1.3 eq.). The mixture was warmed to room temperature and after 2 h H_2O (10 mL) was added. Then the mixture was extracted with Et_2O (4 × 10 mL), the organic extracts were washed with aq. NaCl (10%, 15 mL) and sat. aq. NaCl (10 mL). Drying ($MgSO_4$), removal of the solvent *in vacuo* and purification of the crude product by flash column chromatography [Isohexane] afforded **157** (290 mg, 49%) as a colorless oil.

R_f: 0.54 (Isohexane: EtOAc 16:1).

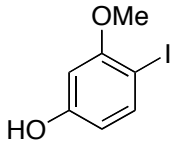
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (d, J = 8.5 Hz, 1H), 6.41 (d, J = 2.6 Hz, 1H), 6.34 (dd, J = 8.5, 2.6 Hz, 1H), 3.85 (s, 3H), 0.98 (s, 9H), 0.20 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.6, 156.4, 133.2, 113.4, 105.2, 103.2, 56.3, 25.8, 18.4, –4.3 ppm.

IR (ATR): $\tilde{\nu}$ = 2954 (m), 2929 (m), 1587 (m), 1202 (s), 975 (s), 834 (s), 778 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{13}H_{21}BrO_2Si^+$ $[M^\bullet]^+$: 316.0494,
found: 316.0486.

4-iodo-3-methoxyphenol (159)[69]



To a stirred solution of 3-methoxyphenol **158** (4.00 g, 32.2 mmol, 1 eq.) in MeOH (100 mL) was added NaOH (1.29 g, 32.2 mmol, 1 eq.) and NaI (4.83 g, 38.6 mmol, 1 eq.) and the mixture was cooled to 0 °C. Bleach (containing 13% active chlorine, 22.1 g, corresponding to 2.87 g, 38.6 mmol, 1.2 eq. NaOCl) was added dropwise over a period of 1 h. After addition the mixture was warmed to room temperature, stirred for 45 min and sat. aq. $Na_2S_2O_3$ (40 mL) was added. The mixture was acidified with aq. HCl (2 M) to pH 6. The solids were removed and washed with Et_2O (30 mL). The organic phase of the filtrate was removed and the aqueous phase was extracted with Et_2O (100 mL, 50 mL). The combined organic phases were washed with H_2O (30 mL), sat. aq. NaCl (100 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and purification of the crude product by flash column chromatography [CH_2Cl_2: Isohexane 3:7 → 1:1] afforded iodide **159** (1.95 g, 41%) as a slightly pink solid.

R_f: 0.52 (Isohexane: EtOAc 7:3).

mp (CH_2Cl_2): 66.4 – 70.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 8.4 Hz, 1H), 6.40 (d, J = 2.6 Hz, 1H), 6.26 (dd, J = 8.4, 2.6 Hz, 1H) 5.24 (s, 1H, *O*H), 3.83 (s, 3H) ppm.

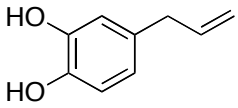
^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 157.4, 139.5, 109.7, 99.9, 74.6, 56.4 ppm.

IR (ATR): $\tilde{\nu}$ = 3351 (m), 2975 (w), 2941 (w), 1581 (s), 1194 (s), 1033 (s), 1016 (s), 826 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_7H_6IO_2^-$ $[M–H]^-$: 248.9418,

found: 248.9420.

4-allylbenzene-1,2-diol (161)[50]



To a stirred suspension of IBX (7.50 g, 26.8 mmol, 2.2 eq.) in THF (150 mL) was added eugenol (**160**) (2.00 g, 12.2 mmol, 1 eq.) and the mixture was stirred in the dark for 24 h. Then a solution of $Na_2S_2O_4$ (12.7 g, 73.2 mmol. 6.0 eq.) in H_2O (50 mL) was added and stirring in the dark was continued for 2 h 30 min. Then phases were separated and sat. aq. NH_4Cl (20 mL) was added to the aqueous phase. The aqueous phase was extracted with Et_2O (2 × 20 mL) and the combined organic phases were concentrated *in vacuo*. The residue was resuspended in EtOAc (100 mL), filtered, washed with sat. aq. $NaHCO_3$ (3 × 50 mL), H_2O (30 mL), sat. aq. NaCl (30 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 4:1] to afford allylcatechol **161** (1.19 g, 65%) as a pale red solid.

R_f: 0.47 (Isohexane:EtOAc).

mp (EtOAc): 42.8 – 43.7 °C.

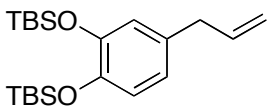
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.80 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 2.0 Hz, 1H), 6.64 (dd, J = 8.0, 2.0 Hz, 1H), 5.92–5.86 (m, 1H), 5.41 (s, 2H, *O*H), 5.09–5.03 (m, 2H), 3.27 (d, J = 6.7 Hz, 2H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 141.8, 137.8, 133.6, 121.3, 116.0, 115.8, 115.6, 39.7 ppm.

IR (ATR): $\tilde{\nu}$ = 3242 (w), 2895 (w), 1603 (w), 1515 (w), 1252 (s), 1185 (s), 1109 (s), 787 (s) cm^{-1}.

HRMS (ESI): calculated for $C_9H_9O_2^-$ $[M–H]^-$: 149.0608
found: 149.0608.

((4-allyl-1,2-phenylene)bis(oxy))bis(*tert*-butyldimethylsilane) (162)[70]



To a stirred mixture of allylcatechol **161** (1.19 g, 7.92 mmol, 1 eq.) in DMF (15 mL) was added TBSCl (2.80 g, 19.0 mmol, 2.4 eq.), imidazole (2.59 g, 38.0 mmol. 4.8 eq.) and 4-dimethylaminopyridine (232 mg, 1.90 mmol, 24 mol-%) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 4 h. After completion, H_2O (30 mL) was added and the biphasic mixture was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with aq. NaCl (10%, 2 × 20 mL), sat. aq. NaCl (20 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography [Isohexane] to afford allyl species **162** (2.43 g, 81%) as a colorless oil.

R_f: 0.21 (Isohexane).

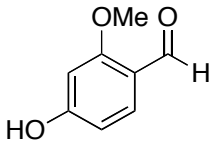
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.75 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 2.2 Hz, 1H), 6.61 (dd, J = 8.0, 2.2 Hz, 1H), 6.00–5.87 (m, 1H), 5.07–5.02 (m, 2H), 3.26 (d, J = 6.7 Hz, 2H), 1.00 (s, 9H), 1.00 (s, 9H), 0.20 (s, 6H), 0.20 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 146.8, 145.2, 138.0, 133.3, 121.7, 121.5, 121.0, 115.5, 39.7, 26.2 (2C), 18.7, 18.7, –3.9, –3.9 ppm.

IR (ATR): $\tilde{\nu}$ = 2928 (w), 2857 (w), 1576 (w), 1507 (s), 1251 (s), 902 (s), 835 (s), 777 (s) cm^{-1}.

HRMS (EI):	calcd. for $C_{21}H_{38}O_2Si_2^+$ $[M]^+$:	378.2405,
	found	378.2404.

4-hydroxy-2-methoxybenzaldehyde (184)[71]



To a stirred suspension of NaH (60%, 77 mg, 3.20 mmol, 2 eq.) in dry THF (20 mL) was added 4-iodo-3-methoxyphenol **159** (400 mg, 1.60 mmol, 1 eq.). After 30 min the mixture was cooled to –78 °C and *n*-BuLi (2.49 M in hexane, 1.29 mL, 3.20 mmol, 2 eq.) was added dropwise. After 40 min dry DMF (0.370 mL, 4.80 mmol, 3 eq.) was added dropwise, the mixture warmed to 0 °C and stirred for 1 h. Sat. aq. NH_4Cl (4 mL) and H_2O (20 mL) were added at 0 °C. The mixture was extracted with EtOAc (3 × 40 mL), the organic extracts washed with sat. aq. NaCl (40 mL) and dried ($MgSO_4$). Removal of the solvent *in vacuo* and purification of the crude product by flash column chromatography [Isohexane: EtOAc 4:1 → 0:1) afforded benzaldehyde **184** (157 mg, 64%) as a pale yellow solid.

R_f: 0.17 (Isohexane: EtOAc 7:3).

mp (EtOAc): 152.0 – 155.0 °C.

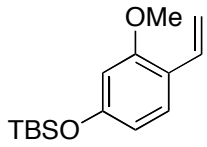
^{1}H NMR (400 MHz, d_6-acetone): δ 10.23 (d, J = 0.8 Hz, 1H), 9.35 (s, 1H, *O*H), 7.64 (d, J = 8.5 Hz, 1H), 6.57 (d, J = 2.1 Hz, 1H), 6.53 (ddd, J = 8.5, 2.1, 0.8 Hz, 1H), 3.91 (s, 3H) ppm.

^{13}C NMR (400 MHz, d_6-acetone): δ 187.3, 165.6, 165.1, 130.7, 119.1, 109.1, 99.7, 56.1 ppm.

IR (ATR): $\tilde{\nu}$ = 3135 (m), 1658 (m), 1569 (s), 1266 (s), 1245 (s), 1208 (s), 837 (s) cm^{-1}.

HRMS (EI): calcd. for $C_8H_8O_3^+$ $[M^{\bullet}]^+$: 152.0473,
found: 152.0475.

tert-butyl(3-methoxy-4-vinylphenoxy)dimethylsilane (185)



To a stirred mixture of Ph_3PMeBr (54.0 mg, 0.150 mmol, 1 eq.) and THF (1.5 mL) was added *n*-BuLi (2.49 M in hexane, 60.0 µL, 0.150 mmol, 1 eq.) dropwise at 0 °C. After 1 h 30 min benzaldehyde **125** (40.0 mg, 0.150 mmol, 1 eq.) was added and the mixture was slowly warmed to room temperature over a period of 3 h 30 min. Then sat. aq. NH_4Cl (3 mL) was added dropwise at 0 °C. After addition of H_2O the mixture was extracted with CH_2Cl_2 (3 × 3 mL) and the organic extracts were dried ($MgSO_4$). Removal of the solvent *in vacuo* and purification of the crude product by flash column chromatography [Isohexane: EtOAc 1:0 → 50:1) afforded styrene **185** (25.0 mg, 63%) as a yellow oil

R_f: 0.50 (Isohexane: EtOAc 16:1).

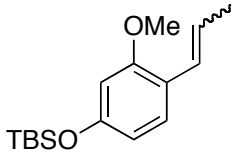
^{1}H NMR (400 MHz, d_6-acetone): δ 7.38 (d, J = 8.3 Hz, 1H), 6.92 (dd, J = 17.8, 11.2 Hz, 1H), 6.49 (d, J = 2.3 Hz, 1H), 6.46 (dd, J = 8.3 Hz, 2.3 Hz, 1H), 5.63 (dd, J = 17.8, 1.7 Hz, 1H), 5.08 (dd, J = 11.2, 1.7 Hz, 1H), 3.82 (s, 3H), 1.00 (s, 9H), 0.23 (s, 6H) ppm.

^{13}C NMR (100 MHz, d_6-acetone): δ 158.8, 157.6, 132.2, 127.7, 120.9, 112.8, 112.3, 104.4, 55.8, 26.0, 18.8, –4.3 ppm.

IR (ATR): $\tilde{\nu}$ = 2930 (w), 2858 (w), 1603 (m), 1572 (w), 1201 (s), 977 (s), 837 (s), 778 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{15}H_{24}O_2Si^+$ $[M^\bullet]^+$: 264.1546,
found: 264.1539.

3-methoxy-4-(prop-1-en-1-yl)phenol (165)



To a stirred mixture of Ph_3PEtBr (3.99 g, 10.8 mmol, 1.4 eq.) in THF (40 mL) was added *n*-BuLi (2.49 M in hexane, 4.23 mL, 10.5 mmol, 1.4 eq.) dropwise at 0 °C. After 1 h benzaldehyde **125** (2.00 g, 7.52 mmol, 1 eq.) was added and the reaction mixture was slowly allowed to warm to room temperature over a period of 2 h. After completion, the reaction was quenched by slow addition of sat. aq. NH_4Cl (40 mL) at

0 °C and the mixture was diluted with H_2O (20 mL). The mixture was extracted with Et_2O (3 × 80 mL) and the combined organic extracts were washed with sat. aq. NaCl (20 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography [Isohexane:EtOAc 60:1] to afford propenephenol **165** (1.32 g, 63%) in a *E/Z* ratio of 2.1:1 as a pale yellow oil.

For characterization purposes a pure sample of the E- isomer was obtained by repeated flash column chromatography and evaluated; subsequent reactions were carried out with the 2.1:1 E/Z mixture!

R_f: 0.30 (Isohexane: EtOAc 16:1).

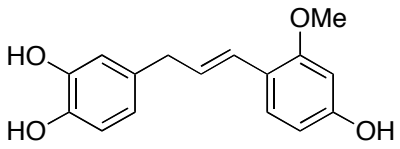
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, J = 8.3 Hz, 1H), 6.61 (dd, J = 15.8, 1.8 Hz, 1H), 6.39 (ddd, J = 8.3, 2.3, 0.4 Hz, 1H), 6.35 (d, J = 2.3 Hz, 1H), 6.10 (dq, J = 15.8, 6.6 Hz, 1H), 3.80 (s, 3H), 1.87 (dd, J = 6.6, 1.8 Hz, 3H), 0.98 (s, 9H), 0.20 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 155.9, 127.1, 125.5, 124.7, 120.8, 112.2, 103.8, 55.6, 25.9, 19.1, 18.5, –4.1 ppm.

IR (ATR): $\tilde{\nu}$ = 2954 (s), 2928 (s), 2856 (s), 1601 (s), 1498 (s), 1289 (w), 1252 (s), 1200 (s), 1161 (s), 977 (s), 836 (s), 777 (s) cm^{-1}.

HRMS (EI): calc. for $C_{16}H_{26}O_2Si^+$ $[M^\bullet]^+$: 278.1697,
found: 278.1694.

(*E*)-4-(3-(4-hydroxy-2-methoxyphenyl)allyl)benzene-1,2-diol (120)



To a stirred solution of TBS protected allylcatechol **162** (985 mg, 2.60 mmol, 2.5 eq.) and propenephenol **165** (290 mg, 1.04 mmol, 1 eq.) in CH_2Cl_2 (7 mL) was added Grubbs 2nd generation catalyst (53.0 mg, 0.062 mmol, 6 mol-%) in one portion and the reaction mixture was heated to 50 °C for 8 h. After completion, silica was added to the reaction mixture and was concentrated *in vacuo*. The crude product was purified by flash column chromatography [Isohexane:EtOAc 30:1] to afford a mixture of TBS protected benzylstyrene and homocoupling products.

To a stirred solution of the mixture of metathesis products (assumed 1.04 mmol) in THF (3 mL) was added TBAF (1 M solution in THF, 3.12 mL, 3.12 mmol, 3.0 eq.) at 0 °C. Reaction mixture was stirred at this temperature for 30 min. After completion, H_2O (4 mL) was added and the biphasic mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with sat. aq. NaCl (3 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [CH_2Cl_2:MeOH 97:3] to afford only benzylstyrene **120** (135 mg, 48% over two steps) as a red oil.

R_f: 0.33 (CH_2Cl_2:MeOH 10:1).

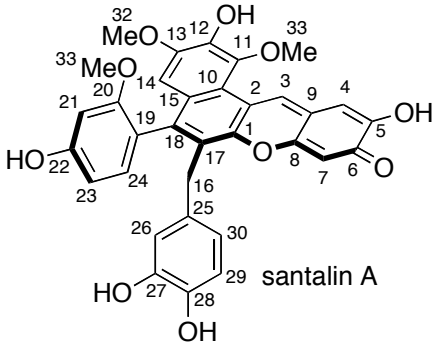
^{1}H NMR (400 MHz, d_3-MeCN): δ 7.24 (d, J = 8.3 Hz, 1H), 6.73 (d, J = 8.1 Hz, 1H), 6.69 (d, J = 1.9 Hz, 1H), 6.60 – 6.56 (m, 2H), 6.41 (d, J = 2.3 Hz, 1H), 6.35 (ddd, J = 8.3, 2.3, 0.4 Hz, 1H), 6.16 (dt, J = 15.9, 7.0 Hz, 1H), 3.77 (s, 3H), 3.35 (dd, J = 7.0, 1.5 Hz, 2H) ppm.

^{13}C NMR (100 MHz, d_3-MeCN): δ 159.0, 158.8, 145.8, 144.1, 134.5, 129.0, 128.6, 126.2, 121.5, 119.7, 116.9, 116.6, 108.6, 100.3, 56.5, 40.0 ppm.

IR (ATR): $\tilde{\nu}$ = 3320 (m), 2974 (m), 2894 (w), 1608 (m), 1504 (s), 1279 (s), 1193 (s), 1106 (s), 954 (s), 831 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{16}H_{15}O_4^+$ $[M–H]^+$: 271.0965,
found: 271.0964.

santalin A (17)



Benzylstyrene **120** (5.00 mg, 18.0 µmol, 1 eq.) and anhydrobase **30** (15.0 mg, 47.0 µmol, 2.6 eq.) were dissolved in MeCN/MeOH (5:1, 0.6 mL). The reaction vessel was sealed and heated to 80 °C for 11 h. After this time, an orange precipitate formed and was collected from the reaction mixture by transferring the mixture to an Eppendorf tube and by sedimentation with a centrifuge. The precipitate was washed with MeOH (2 × 0.2 mL) and santalin A (**17**) (7.00 mg, 67 %) could be obtained as a dark red powder.

R_f: 0.24 (CH_2Cl_2:MeOH 10:1).

UV (CH_2Cl_2): λ_{max} = 443, 470, 502 nm.

mp (MeOH): 278 °C decomp.

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.74 (s, 1H, *O*H), 9.60 (s, 1H, *O*H), 9.51 (s, 1H), 9.28 (s, 1H, *O*H), 8.61 (s, 1H, *O*H), 8.51 (s, 1H, *O*H), 7.06 (s, 1H), 6.96 (d, J = 8.1 Hz, 1H), 6.65 (s, 1H), 6.62 (d, J = 2.2 Hz, 1H), 6.55 (dd, J = 8.2, 2.2 Hz, 1H), 6.51 (d, J = 8.2 Hz, 1H), 6.51 (d, J = 2.2 Hz, 1H), 6.37 (d, J = 1.2 Hz, 1H), 6.34 (dd, J = 8.2, 2.2 Hz, 1H), 3.93 (d, J = 14.7 Hz, 1H), 3.89 (s, 3H), 3.79 (d, J = 14.7 Hz, 1H), 3.63 (s, 3H), 3.58 (s, 3H) ppm.

^{13}C NMR (100 MHz, d_6-DMSO): δ 177.3, 158.9, 157.6, 156.0, 152.2, 149.0, 148.4, 144.7, 143.5, 143.1, 141.3, 141.3, 133.6, 131.5, 130.9, 125.9, 124.6, 121.3, 119.1, 116.9, 116.6, 115.9, 115.2, 113.1, 107.4, 105.1, 103.4, 101.2, 99.4, 59.5, 55.4, 55.1, 33.1 ppm.

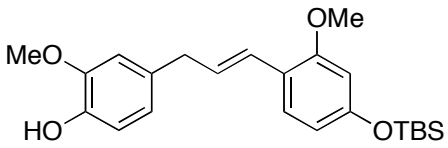
IR (ATR): $\tilde{\nu}$ = 3166 (m), 2923 (m), 2897 (m), 2362 (w), 1551 (m), 1497 (s), 1456 (s), 1344 (s), 1293 (s), 1201 (s), 1023 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{33}H_{27}O_{10}^{+}$ $[M+H]^{+}$: 583.1599,
found: 583.1607.

Number	^{1}H (Synthetic)	^{13}C (Synthetic)	^{1}H (Isolated)[2]	^{13}C (Isolated)[2]
*O*H	9.74 (s)		-	
*O*H	9.60 (s)		-	
*O*H	9.28 (s)		-	
*O*H	8.61 (s)		-	
*O*H	8.51 (s)		-	
1		149.0		149.0
2		113.1		113.1
3	9.51 (s)	133.6	9.52 (d, J = 0.4 Hz)	133.6
4	7.06 (s)	105.1	7.06 (d, J = 0.4 Hz)	104.9
5		152.2		152.1
6		177.3		177.2
7	6.37 (d, J = 1.2 Hz)	101.2	6.38 (d, J = 1.3 Hz)	101.1
8		156.0		156.0
9		121.3		121.2
10		116.9		116.9
11		143.5		143.5
12		141.3		141.2

13		148.4		148.3
14	6.65 (s)	103.4	6.67 (s)	103.4
15		124.6		124.6
16	3.79, 3.93 (ABq, *J* = 14.7 Hz)	33.1	3.82, 3.95 (ABq, *J* = 14.8 Hz)	33.0
17		125.9		125.9
18		141.3		141.3
19		157.6		157.7
20		99.4		99.3
21	6.62 (d, *J* = 2.2 Hz)	158.9	6.65 (d, J = 2.2 Hz)	158.9
22		107.4		107.3
23	6.55 (d, *J* = 8.2, 2.2 Hz)	131.5	6.57 (dd, *J* = 8.2, 2.2 Hz)	131.4
24	6.96 (d, *J* = 8.2 Hz)	116.6	6.97 (d, *J* = 8.2 Hz)	116.6
25		130.9		130.9
26	6.51 (s)	115.9	6.54 (d, *J* = 2.2 Hz)	115.8
27		144.7		144.6
28		143.1		143.0
29	6.51 (d, *J* = 8.1 Hz)	115.2	6.54 (d, *J* = 8.2 Hz)	115.1
30	6.34 (dd, *J* = 8.2, 2.2 Hz)	119.1	6.36 (dd, *J* = 8.2, 2.2 Hz)	119.1
31	3.89 (s)	59.5	3.91 (s)	59.4
32	3.63 (s)	55.4	3.65 (s)	55.3
33	3.58 (s)	55.1	3.59 (s)	55.0

(*E*)-4-(3-(4-((*tert*-butyldimethylsilyl)oxy)-2-methoxyphenyl)allyl)-2-methoxyphenol (166)



To a stirred solution of eugenol (**160**) (354 mg, 2.16 mmol, 3 eq.) and propenephenol **165** (200 mg, 0.720 mmol, 1 eq.) in CH_2Cl_2 (6 mL) was added Grubbs 2nd generation catalyst (61.0 mg, 0.0700 mmol, 0.1 eq.) in one portion and the reaction mixture was heated at 50 °C for 8 h. After completion, silica was added to the reaction mixture and was concentrated *in vacuo*. The crude product was purified by flash column chromatography [Isohexane:EtOAc 10:1] to afford benzylstyrene **166** (244 mg, 85%) as a dark-yellow oil.

R_f: 0.28 (Isohexane: EtOAc 7:1).

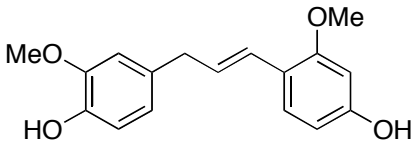
^{1}H NMR (600 MHz, d_3-MeCN): δ 7.26 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 2.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.68 (dd, J = 8.0, 2.0 Hz, 1H), 6.62 (d, J = 15.8 Hz, 1H), 6.44 (d, J = 2.2 Hz, 1H), 6.40 (dd, J = 8.3, 2.2 Hz, 1H), 6.32 (s, 1H, *O*H), 6.24 (td, J = 15.8, 7.0 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.43 (dd, J = 7.0, 1.5 Hz, 2 H), 0.99 (s, 9H), 0.20 (s, 6H) ppm.

^{13}C NMR (150 MHz, d_3-MeCN): δ 158.8, 157.45, 148.6, 145.7, 133.9, 129.9, 128.4, 126.1, 122.2, 121.4, 116.0, 113.5, 113.4, 105.1, 57.0, 56.6, 40.3, 26.4, 19.3, –3.8 ppm.

IR (ATR): $\tilde{\nu}$ = 3423 (w), 2954 (m), 2928 (m), 2856 (m), 1601 (s), 1499 (s), 1462 (m), 1287 (s), 1199 (s), 975 (s), 834 (s), 778 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{23}H_{31}O_4Si^+$ $[M–H]^+$: 399.1986,
found: 399.1988.

(*E*)-4-(3-(4-hydroxy-2-methoxyphenyl)allyl)-2-methoxyphenol (167)



To a stirred solution of metathesis product **166** (87.0 mg, 0.220 mmol, 1 eq.) in THF (2 mL) was added TBAF (1 M solution in THF, 262 µL, 0.260 mmol, 1.2 eq.) at 0 °C. The reaction mixture was stirred at this temperature for 30 min and after completion, H_2O (3 mL) was added. The reaction mixture was extracted with Et_2O (3 × 8 mL) and combined organic extracts were washed with sat. aq. NaCl (2 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [CH_2Cl_2:MeOH 99:1] to afford benzylstyrene **167** (30.0 mg, 48%) as a yellow oil.

R_f: 0.47 (CH_2Cl_2: MeOH 10:1).

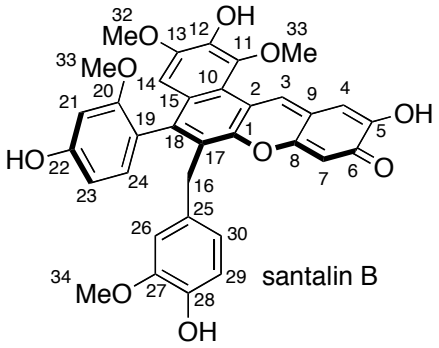
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, J = 8.4 Hz, 1H), 6.94 (br, 1H, *O*H) 6.83 (d, J = 1.9 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.68 (dd, J = 8.0, 1.9 Hz, 1H), 6.60 (dt, J = 15.9, 1.5 Hz, 1H), 6.41 (d, J = 2.3 Hz, 1H), 6.34 (ddd, J = 8.4, 2.3, 0.4 Hz, 1H), 6.30 (br, 1H, *O*H), 6.20 (dt, J = 15.9, 7.0 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), (dd, J = 7.0, 1.5 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 158.8, 148.5, 145.7, 134.1, 129.0, 128.7, 126.2, 122.2, 119.7, 115.9, 113.4, 108.6, 100.3, 57.0, 56.5, 40.3 ppm.

IR (ATR): $\tilde{\nu}$ = 3378 (m), 2936 (m), 2836 (w), 1599 (s), 1504 (s), 1462 (s), 1429 (s), 1266 (s), 1194 (s), 1154 (s), 1030 (s), 954 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{17}H_{17}O_4^+$ $[M–H]^+$: 285.1121,
found: 285.1129.

santalin B (18)



Benzylstyrene **167** (4.00 mg, 14.0 μmol, 1 eq.) and anhydrobase **30** (11.0 mg, 35.0 μmol, 2.5 eq.) were dissolved in MeCN/MeOH (5:1, 0.6 mL). The reaction vessel was sealed and was heated for 12 h. After this time, the reaction mixture was concentrated *in vacuo*. Purification by Sephadex column chromatography (LH-20, MeOH) afforded santalin B (**18**) (5.00 mg, 62%) as a dark red oil.

R_f: 0.33 (CH_2Cl_2: MeOH 10:1).

UV (CH_2Cl_2): λ_{max} = 447, 470, 502 nm.

^{1}H NMR (600 MHz, d_6–DMSO): δ 9.77 (s, 1H, *O*H), 9.61 (s, 1H, *O*H), 9.51 (s, 1H), 9.28 (s, 1H, *O*H), 8.62 (s, 1H, *O*H), 7.06 (s, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.66 (s, 1H), 6.65 (d, *J* = 2.2 Hz, 1H), 6.63 (d, *J* = 1.9 Hz, 1H), 6.56 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 2H), 6.51 (d, *J* = 8.2, 1.9 Hz, 1H), 6.42 (d, *J* = 1.1 Hz, 1H), 4.05 (d, *J* = 14.6 Hz, 2H), 3.89 (s, 3H), 3.89 (d, *J* = 14.6 Hz, 1H), 3.64 (s, 3H), 3.63 (s, 3H), 3.59 (s, 3H) ppm.

^{13}C NMR (100 MHz, d_6-DMSO): δ 177.1, 159.0, 157.7, 156.0, 152.1, 148.9, 148.4, 147.0, 144.5, 143.5, 141.3, 141.2, 133.5, 131.6, 130.8, 125.9, 124.6, 121.3, 120.7, 116.9, 116.6, 115.0, 113.2, 112.6, 107.3, 104.9, 103.3, 101.0, 99.6, 59.5, 55.4, 55.4, 55.2, 33.1 ppm.

IR (ATR): $\tilde{\nu}$ = 3142 (m), 3002 (m), 2928 (m), 1608 (m), 1550 (m), 1494 (s), 1460 (s), 1433 (s), 1288 (s), 1257 (s), 1083 (s), 1007 (s) cm^{-1}.

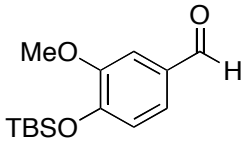
HRMS (ESI): calcd. for $C_{34}H_{29}O_{10}^{+}$ $[M+H]^{+}$: 597.1755,
found: 597.1762.

Number	^{1}H (synthetic)	^{13}C (Synthetic)	^{1}H (Isolated)[2]	^{13}C (Isolated)[2]
*O*H	9.77 (s)		-	
*O*H	9.61 (s)		-	
*O*H	9.28 (s)		-	
*O*H	8.62 (s)		-	
1		148.9		148.9
2		113.2		113.1
3	9.51 (s)	133.5	9.52 (d, *J* = 0.3 Hz)	133.6
4	7.06 (s)	104.9	7.07 (d, *J* = 0.3 Hz)	105.0
5		152.1		152.1
6		177.1		177.2
7	6.42 (d, *J* = 1.1 Hz)	101.0	6.44 (d, *J* = 1.0 Hz)	101.1
8		156.0		156.0
9		121.3		121.2
10		116.9		116.9
11		143.5		143.5
12		141.3		141.3
13		148.4		148.3
14	6.66 (s)	103.3	6.68 (s)	103.4
15		124.6		124.5
16	3.89, 4.05 (ABq, *J* = 14.6 Hz)	33.1	3.90, 4.05 (ABq, *J* = 14.5 Hz)	33.0
17		125.9		125.8
18		141.2		141.2
19		157.7		157.7
20		159.0		159.0
21	6.65 (d, *J* = 2.2 Hz)	99.6	6.67 (d, *J* = 2.2 Hz)	99.5
22		116.6		116.6
23	6.57 (dd, *J* = 8.3, 2.2 Hz)	107.3	6.59 (dd, *J* = 8.3, 2.0 Hz)	107.4
24	6.98 (d, *J* = 8.2 Hz)	131.6	7.00 (d, *J* = 8.3 Hz)	131.7
25		130.8		130.8
26	6.63 (d, *J* = 1.9 Hz)	112.6	6.65 (d, *J* = 1.9 Hz)	112.7

27		147.0		147.0
28		144.5		144.4
29	6.56 (d, *J* = 8.2 Hz)	115.0	6.59 (d, *J* = 8.2 Hz)	115.1
30	6.51 (dd, *J* = 8.2, 1.9 Hz)	120.7	6.36 (dd, *J* = 8.2, 1.9 Hz)	120.6
31	3.89 (s)	59.5	3.91 (s)	59.4
32	3.63 (s)	55.4	3.65 (s)	55.3
33	3.59 (s)	55.2	3.59 (s)	55.2
34	3.64 (s)	55.4	3.66 (s)	55.4

V. 6. Experimental towards santarubin A and B

4-((*tert*-butyldimethylsilyl)oxy)-3-methoxybenzaldehyde (172)[72]



To a stirred mixture of vanillin (**171**) (6.00 g, 39.4 mmol, 1 eq.) in dry DMF (30 mL) was added TBSCl (7.15 g, 47.3 mmol, 1.2 eq.) and imidazole (6.44 g, 94.6 mmol, 2.40 eq.) at 0 °C. After 30 min the mixture was warmed to room temperature and stirring continued for 4 h 30 min. After completion H_2O (20 mL) was added and the reaction mixture was extracted with Et_2O (3 x 50 mL) and the organic extracts were washed with aq. NaCl (10%, 2 x 20 mL), sat. aq. NaCl (20 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane: EtOAc 30:1) to afford benzaldehyde **172** (10.4 g, 98%) as a colorless oil.

R_f: 0.27 (Isohexane: EtOAc 16:1).

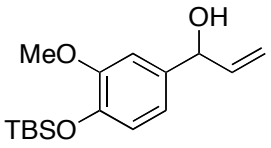
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.40 (d, J = 1.9 Hz, 1H), 7.37 (dd, J = 8.0, 1.9 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 3.87 (s, 3H), 1.00 (s, 9H), 0.19 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 191.2, 151.9, 151.6, 131.2, 126.4, 120.9, 110.4, 55.7, 25.8, 18.7, –4.3 ppm.

IR (ATR): $\tilde{\nu}$ = 2954 (m), 2929 (m), 2885 (w), 2856 (m), 1695 (s), 1683 (s), 1592 (s), 1505 (s), 1463 (s), 1283 (s), 1233 (s), 1150 (s), 894 (s), 838 (s), 779 (s) cm^{-1}.

HRMS (EI): calcd. for $C_{14}H_{21}O_3Si^+$ $[M^\bullet]^+$: 265.1254,
found: 265.1261.

1-(4-((*tert*-butyldimethylsilyl)oxy)-3-methoxyphenyl)prop-2-en-1-ol (169)



To a stirred solution of benzaldehyde **172** (6.00 g, 22.5 mmol, 1 eq.) in THF (50 mL) was added vinylmagnesiumbromide (1 M solution in THF, 27.0 mL, 27.0 mmol, 1.2 eq.) at 0 °C. The reaction mixture was stirred for 1 h 50 min at this temperature and upon completion, aq. sat. NH_4Cl (30 mL) was added. The reaction mixture was extracted with Et_2O (3 × 60 mL) and the combined organic extracts were washed with sat. aq. NaCl (20 ml) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 8:1) to afford allylic alcohol **169** (5.36 g, 81%) as a colorless oil.

R_f: 0.25 (Isohexane:EtOAc 7:1).

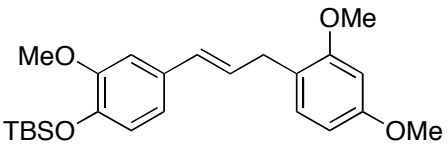
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 – 6.80 (m, 3H), 6.06 (ddd, J = 17.1, 10.3, 5.8 Hz, 1H), 5.34 (dt, J = 17.1, 1.5 Hz, 1H), 5.20 (dt, J = 10.3, 1.5 Hz, 1H), 5.14 (d, J = 5.8 Hz, 1H), 3.81 (s, 3H), 1.00 (s, 9H), 0.16 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 151.3, 144.9, 104.5, 136.3, 121.0, 119.0, 115.1, 110.5, 75.4, 55.7, 25.9, 18.7, –4.4 ppm.

IR (ATR): $\tilde{\nu}$ = 3358 (w), 2954 (s), 2929 (s), 2856 (s), 1510 (s), 1279 (s), 1249 (s), 1230 (s), 916 (s), 838 (s), 779 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{16}H_{25}O_3Si^-$ $[M–H]^-$: 293.1578,
found: 293.1575.

(*E*)-((4-(3-(2,4-dimethoxyphenyl)prop-1-en-1-yl)-1,2-phenylene)bis(oxy))bis(*tert*-butyldimethylsilane) (173)



To a solution of allylic alcohol **169** (1.18 mg, 3.00 mmol, 1 eq.) and *O,O'*-dimethylresorcinol **170** (1.24 mg, 9.00 mmol, 3 eq.) in CH_2Cl_2 (20 mL) was added successively molecular sieves 4 Å (1.00 g) and $Cu(OTf)_2$ (110 mg, 300 µmol, 10 mol-%) at 0 °C and the reaction mixture was stirred at this temperature for 30 min. Upon completion, sat. aq. NH_4Cl (30 mL) was added and the mixture was extracted with Et_2O (3 × 70 mL). The combined organic extracts were washed with sat. aq. NaCl (30 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 80:1] to afford benzylstyrene **173** (1.00 g, 81%) as a colorless oil.

R_f: 0.27 (Isohexane:EtOAc 16:1).

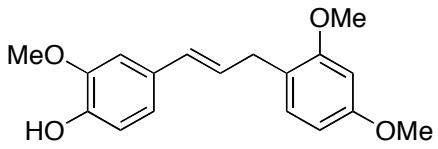
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (d, J = 8.1 Hz, 1H), 6.87 (d, J = 1.8 Hz, 1H), 6.81 (dd, J = 8.2, 1.9 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 6.48 (d, J = 2.3 Hz, 1H), 6.45 (dd, J = 8.1, 2.4 Hz, 1H), 6.33 (d, J = 15.8 Hz, 1H), 6.20 (dt, J = 15.7, 6.4 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.45 (d, J = 6.3 Hz, 2H), 1.00 (s, 9H), 0.15 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 158.4, 151.1, 144.5, 132.1, 130.4, 130.3, 127.6, 121.5, 121.1, 119.2, 109.8, 104.2, 98.8, 55.7, 55.7, 55.6, 32.8, 26.0, 18.7, –4.4 ppm.

IR (ATR): $\tilde{\nu}$ = 2998 (w), 2953 (m), 2929 (m), 2902 (m), 1612 (m), 1505 (s), 1463 (m), 1277 (s), 1206 (s), 1153 (s), 1123 (s), 1036 (s), 893 (s), 835 (s), 780 (s) cm^{-1}.

HRMS (ESI): calc. for $C_{24}H_{33}O_4Si^+$ $[M–H]^+$: 413.2143,
found: 413.2145.

(*E*)-*tert*-butyl(4-(3-(2,4-dimethoxyphenyl)prop-1-en-1-yl)-2-methoxyphenoxy)dimethylsilane (168)



To a stirred solution of styrene **173** (200 mg, 480 μmol, 1 eq.) in THF (4 mL) was added TBAF (1 M solution in THF, 580 μL, 580 μmol, 1.2 eq.) at 0 °C. The reaction mixture was stirred for 30 min at this temperature and after completion, the reaction mixture was quenched by addition of H_2O (10 mL) and the biphasic mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with sat. aq. NaCl (5 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [CH_2Cl_2:MeOH 99:1] to afford benzylstyrene **168** (68.0 mg, 47.0 %) as a pale red oil.

R_f: 0.66 (CH_2Cl_2: MeOH 99:1).

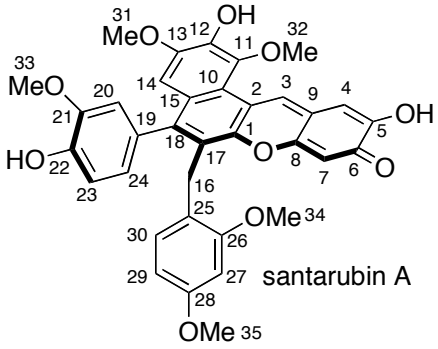
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (d, J = 8.1 Hz, 1H), 6.87 – 6.83 (m, 3H), 6.48 (s, 1H), 6.45 (d, J = 8.1 Hz, 1H) 6.33 (d, J = 16.0 Hz, 1H), 6.19 (dt, J = 16.0, 6.5 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.45 (d, J = 6.5 Hz, 2H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 158.4, 146.7, 145.1, 130.7, 130.3 (2C), 127.3, 121.5, 119.9, 114.5, 108.3, 104.2, 98.9, 56.1, 55.6, 55.6, 32.8 ppm.

IR (ATR): $\tilde{\nu}$ = 3501 (w), 3427 (w), 2958 (m), 2834 (m), 1610 (m), 1587 (m), 1504 (s), 1462 (m), 1260 (s), 1205 (s), 1152 (s), 1117 (s), 1031 (s), 819 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{18}H_{19}O_4^+$ $[M–H]^+$: 299.1278,
found: 299.1277.

santarubin A (19)



Benzylstyrene **168** (6.00 mg, 20.0 µmol, 1 eq.) and anhydrobase **30** (16.0 mg, 50.0 µmol, 2.5 eq.) were dissolved in MeCN/MeOH (5:1, 0.6 mL). The reaction vessel was sealed and heated to 80 °C for 9 h. After this time, an orange precipitate formed, which upon cooling to room temperature could be collected from reaction mixture by transferring the suspension into an Eppendorf tube and sedimentation with a centrifuge. The precipitate was washed with MeOH (2 × 0.3 mL) affording santarubin A (**19**) (10.0 mg, 83%) as a bright red powder.

R_f: 0.42 (CH_2Cl_2:MeOH 10:1).

UV (CH_2Cl_2): λ_{max} = 443, 470, 501 nm.

mp (MeOH): 287 °C decomp.

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.77 (s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 7.01 (s, 1H), 6.81 (s, 1H), 6.77 (dd, J = 8.0, 1.9 Hz, 1H), 6.60 (d, J = 1.9 Hz, 1H), 6.58 (s, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.42 (d, J = 2.4 Hz, 1H), 6.22 (dd, J = 8.4, 2.4 Hz, 1H), 4.16 (d, J = 15.9 Hz, 1H), 4.06 (s, 3H), 4.03 (d, J = 15.9 Hz, 1H), 3.78 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H), 3.65 (s, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 176.3 (*), 159.6, 158.0, 157.4, 151.6, 150.9 (*), 147.4, 146.6, 146.2, 145.5, 143.4, 140.5, 136.8 (**), 130.0, 128.8, 126.2, 125.9, 122.7, 122.0, 121.2, 117.8, 114.7, 112.2, 106.3 (**), 104.5 (**), 104.1, 104.1, 101.6, 98.4, 60.4, 56.3, 56.0, 55.7, 55.5, 27.1 ppm.

(*) obscured carbon was detected by HMBC
(**) obscured carbon was detected by HSQC

IR (ATR): $\tilde{\nu}$ = 3278 (w), 2934 (w), 2836 (w), 1570 (m), 1496 (s), 1456 (s), 1342 (s), 1291 (s), 1200 (s), 1073 (s), 1119 (m), 1037 (s), 825 (s) cm^{-1}.

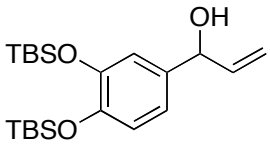
HRMS (ESI): calcd. for $C_{35}H_{31}O_{10}^{+}$ $[M+H]^{+}$: 611.1912,
found: 611.1903.

Number	^{1}H (Synthetic)	^{13}C (Synthetic)	^{1}H (Isolated)[1]
1		150.9	
2		106.3	
3	9.77 (s, 1H)	136.5	9.66 (1H)
4	7.01 (s, 1H)	104.5	7.1–6.1 (m, 9H)***
5		151.6	
6		176.3	
7	6.58 (s, 1H)	101.6	7.1–6.1 (m, 9H)***
8		157.4	
9		122.0	
10		117.8	
11		143.4	
12		140.5	
13		147.4	
14	6.81 (s, 1H)	104.1	7.1–6.1 (m, 9H)***
15		125.9	
16	4.16, 4.03	27.1	4.01 (2H)

	(ABq, *J* = 15.9 Hz, 2H)		
17		126.2	
18		146.2	
19		130.0	
20	6.60 (d, J = 1.9 Hz, 1H)	112.2	7.1–6.1 (m, 9H)***
21		146.6	
22		145.5	
23	7.02 (d, J = 8.0 Hz, 1H)	114.7	7.1–6.1 (m, 9H)***
24	6.77 (dd, J = 8.0, 1.9 Hz, 1H)	122.7	7.1–6.1 (m, 9H)***
25		121.2	
26		158.0	
27	6.42 (d, J = 2.4 Hz, 1H)	98.4	7.1–6.1 (m, 9H)***
28		159.6	
29	6.22 (dd, J = 8.4, 2.4 Hz, 1H)	104.1	7.1–6.1 (m, 9H)***
30	6.54 (d, J = 8.4 Hz, 1H)	128.8	7.1–6.1 (m, 9H)***
31	3.78 (s, 3H)	56.3	3.78 (3H)
32	4.06 (s, 3H)	60.4	4.06 (3H)
33	3.65 (s, 3H)	56.0	3.66 (3H)
34	3.78 (s, 3H)	55.7	3.78 (3H)
35	3.73 (s, 3H)	55.5	3.74 (3H)

*** 9 aromatic protons were described as a multiplet in the range of 7.1–6.1 ppm

1-(3,4-bis((*tert*-butyldimethylsilyl)oxy)phenyl)prop-2-en-1-ol (174)[54]



To a stirred solution of benzaldehyde **61** (5.44 g, 14.9 mmol, 1 eq.) in THF (71 mL) was added vinylmagnesiumbromide (1 M solution in THF, 17.8 mL, 17.8 mmol, 1.2 eq.) at 0°C. The reaction mixture was stirred for 3 h at 0 °C and upon completion, aq. sat. NH_4Cl (30 mL) was added. The reaction mixture was extracted with Et_2O (3 × 100 mL) and combined organic extracts were washed with sat. aq. NaCl (20 ml) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane: EtOAc 30:1) to afford **174** (4.45 g, 76 %) as colorless oil.

R_f: 0.31 (Isohexane: EtOAc 7:1).

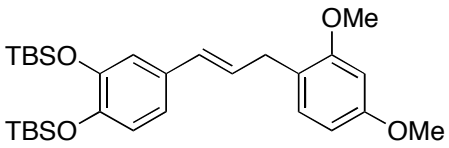
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 – 6.78 (m, 3H) 6.00 (ddd, J = 17.1, 10.4, 5.8 Hz, 1H), 5.28 (dt, J = 17.1, 1.4 Hz, 1H), 5.15 (dt, J = 10.4, 1.4 Hz, 1H), 5.06 (dt, J = 3.8, 1.6 Hz, 1H), 0.97 (s, 9 H), 0.97 (s, 9H), 0.17 (s, 12H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 146.7, 140.5, 136.0, 121.1, 119.6, 119.6, 114.9, 75.0, 26.2 (2C), 26.1, 18.7, –3.9, –3.9, –3.9 ppm.

IR (ATR): $\tilde{\nu}$ = 3416 (w), 2929 (m), 2857 (s), 2359 (m), 1506 (s), 1290 (s), 1252 (s), 1119 (s), 985 (s), 902 (s), 836 (s), 788 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{21}H_{37}O_2Si_2^+$ $[M–OH]^+$: 377.2327,
found: 377.2329.

(*E*)-((4-(3-(2,4-dimethoxyphenyl)prop-1-en-1-yl)-1,2-phenylene)bis(oxy))bis(*tert*-butyldimethylsilane) (175)



To a solution of allylic alcohol **174** (883 mg, 2.24 mmol, 1 eq.) and *O,O'*-dimethylresorcinol **170** (1.24 g, 8.96 mmol, 4 eq.) in CH_2Cl_2 (20 mL) was added successively molecular sieves 4 Å (1.00 g) and $Cu(OTf)_2$ (80.0 mg, 220 µmol, 10 mol-%) at 0 °C. The reaction mixture was stirred at this temperature for 30 min and upon completion, aq. sat. NH_4Cl (30 mL) was added. The reaction mixture was extracted with Et_2O (3 × 70 mL) and the combined organic extracts were washed with sat. aq. NaCl (30 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [Isohexane:EtOAc 40:1] to afford benzylstyrene **175** (725 mg, 63%) as a colorless oil.

R_f: 0.41 (Isohexane:EtOAc 16:1).

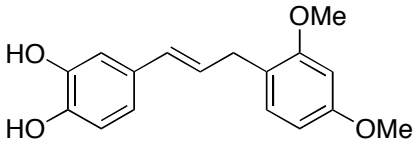
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.07 (d, J = 8.2 Hz, 1H), 6.83 (d, J = 2.2 Hz, 1H), 6.80 (dd, J = 8.2, 2.2 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 6.44 (dd, J = 8.2, 2.4 Hz, 1H), 6.26 (d, J = 15.7 Hz, 1H) 6.15 (dt, J = 15.7, 6.8 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.42 (d, J = 6.8 Hz, 2H), 0.99 (s, 9H), 0.97 (s, 9H), 0.19 (s, 6H), 0.18 (s, 6H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ 159.6, 158.4, 146.9, 146.3, 131.8, 130.2, 130.2, 127.4, 121.6, 121.2, 119.5, 119.0, 104.2, 98.8, 55.6, 55.6, 32.8, 26.2, 26.2, 18.7, 18.7, –3.6, –3.9 ppm.

IR (ATR): $\tilde{\nu}$ = 3362 (w), 2958 (w), 1610 (m), 1503 (s), 1437 (m), 1279 (s), 1205 (s), 1151 (s), 1034 (s), 963 (m), 818 (s), 785 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{29}H_{45}O_4Si_2^+$ $[M–H]^+$: 513.2851,
found: 513.2851.

(*E*)-4-(3-(2,4-dimethoxyphenyl)prop-1-en-1-yl)benzene-1,2-diol (176)



To a stirred solution of styrene **175** (200 mg, 390 µmol, 1 eq.) in THF (4 mL) was added TBAF (1 M solution in THF, 860 µL, 860 µmol, 2.2 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and upon completion, H_2O (10 mL) was added. The reaction mixture was extracted with Et_2O (3 × 25 mL) and the combined organic extracts were washed with sat. aq. NaCl (2 mL) and dried (Na_2SO_4). The crude product was purified by flash column chromatography [CH_2Cl_2:MeOH 98:2 → 95:5] to afford benzylstyrene **176** (79.0 mg, 71%) as a pale yellow oil.

R_f: 0.25 (CH_2Cl_2:MeOH 95:5).

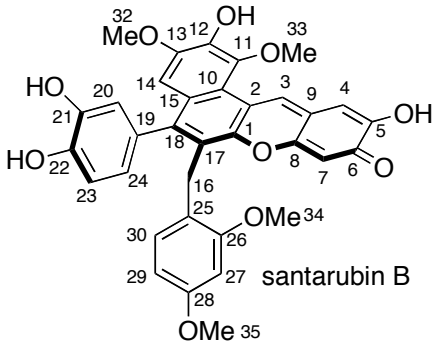
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, J = 8.2 Hz, 1H), 6.84 (d, J = 1.0 Hz, 1H), 6.72 – 6.71 (m, 2H), 6.61 (br, 2H, *O*H), 6.52 (d, J = 2.4 Hz, 1H), 6.46 (dd, J = 8.2, 2.4 Hz, 1H), 6.25 (dt, J = 15.9, 1.1 Hz, 1H), 6.16 (dt, J = 15.9, 6.6 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.36 (d, J = 6.6 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 159.3, 145.6, 144.9, 131.7, 131.1, 130.9, 127.8, 122.0, 119.5, 116.3, 113.5, 105.5, 99.5, 56.2, 56.0, 33.3 ppm.

IR (ATR): $\tilde{\nu}$ = 2952 (m), 2928 (m), 2894 (w), 2856 (m), 1612 (m), 1504 (s), 1470 (m), 1287 (s), 1251 (s), 1206 (s), 1155 (s), 1121 (s), 900 (s) 833 (s), 777 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{17}H_{17}O_4^-$ $[M–H]^-$: 285.1121,
found: 285.1129.

santarubin B (20)



Benzylstyrene **176** (6.00 mg, 20.0 µmol, 1 eq.) and anhydrobase **30** (16.0 mg, 50.0 µmol, 2.5 eq.) were dissolved in MeCN/MeOH (5:1, 0.6 mL). The reaction vessel was sealed and was heated to 80 °C for 10 h. After this time, an orange precipitate formed, which was collected, upon cooling the reaction mixture to room temperature, by transferring the suspension into an Eppendorf tube and sedimentation with a centrifuge. The precipitate was washed with MeOH (2 × 0.3 mL) affording santarubin B (**20**) (9.00 mg, 74%) as a red powder.

R_f: 0.33 (CH_2Cl_2: MeOH 10:1).

mp (MeOH): 272 °C decomp.

UV (CH_2Cl_2): λ_{max} = 443, 469, 501 nm.

^{1}H NMR (600 MHz, d_6-DMSO): δ 9.53 (s, 1H), 9.22 (br, 3H, *O*H), 7.05 (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.76 (s, 1H), 6.65 (d, J = 2.1 Hz, 1H), 6.54 – 6.49 (m, 3H), 6.27 (dd, J = 8.5, 2.4 Hz, 1H), 6.04 (d, J = 1.1 Hz, 1H), 3.98 (d, J = 15.9 Hz, 1H), 3.94 (d, J = 16.0 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.66 (s, 3H), 3.64 (s, 3H) ppm.

^{13}C NMR (150 MHz, d_6-DMSO): δ 177.1, 158.5, 157.3, 156.1, 152.1, 149.0, 148.3, 145.1, 145.0, 144.9, 143.6, 141.4, 133.6, 128.7, 128.1, 124.4, 123.9, 121.3, 120.4, 120.3, 117.2, 116.8, 115.7, 113.0, 105.0, 104.2, 103.9, 101.0, 98.1, 59.5, 55.4, 55.4, 54.9, 26.6 ppm.

IR (ATR): $\tilde{\nu}$ = 3118 (m), 2923 (m), 2893 (w), 2471 (w), 1546 (m), 1497 (s), 1468 (s), 1342 (s), 1295 (s), 1208 (s), 1175 (s), 1151 (s), 1071 (s), 1043 (s) cm^{-1}.

HRMS (ESI): calcd. for $C_{34}H_{29}O_{10}^{+}$ $[M+H]^{+}$: 597.1755,
found: 597.1762.

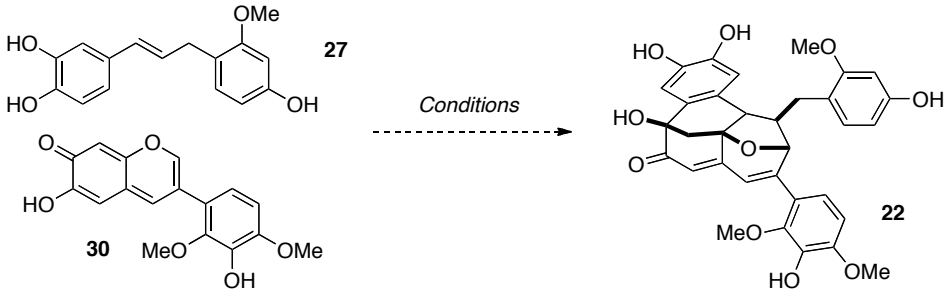
Number	^{1}H (synthetic)	^{13}C (Synthetic)
1		149.0
2		113.0
3	9.53 (s, 1H)	133.6
4	7.05 (s, 1H)	105.0
5		152.1
6		177.1
7	6.04 (d, J = 0.7 Hz, 1H)	101.0
8		156.1
9		121.3
10		117.2
11		143.6
12		141.4
13		148.3
14	6.75 (s, 1H)	103.9
15		124.4
16	4.00, 3.95 (ABq, d, J = 16.0 Hz, 1H)	26.2
17		123.9
18		144.9
19		128.7
20	6.65 (d, J = 2.2 Hz, 1H)	116.8
21		145.1

22		145.0
23	6.85 (d, *J* = 8.1 Hz, 1H)	115.7
24	6.54 – 6.49 (m, 3H)*	120.4
25		120.3
26		157.3
27	6.54 – 6.49 (m, 3H)*	98.1
28		158.5
29	6.27 (dd, *J* = 8.2, 1.5 Hz, 1H)	104.2
30	6.54 – 6.49 (m, 3H)*	128.1
31	3.91 (s, 3H)	55.4
32	3.64 (s, 3H)	59.5
33	3.81 (s, 3H)	55.4
34	3.66 (s, 3H)	54.9

* 3 aromatic H were detected in the range of 6.54–6.49.

VI. Appendix I – Table 10

Table 10 Conditions screened towards the synthesis of santalin Y



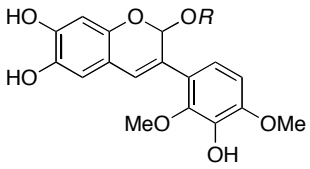
Entry	Ratio 27:30	Solvent	Additive	Light source	Filter	T [° C]	Observation
1	1:1	MeOH	-	RL	Q	12	s.m. + **102**
2	1:1	MeCN/MeOH	-	RL	Q	12	s.m. + **102**
3	1:1	MeCN/H_2O	-	RL	Q	12	s.m. + **102**
4	1:1	MeCN/MeOH	-	RL	Q	12	s.m. + **102**
5	1:1	MeCN/EtOH	-	RL	P	12	s.m. + **102**
6	1:1	EtOH	-	RL	P	12	s.m. + **102**
7	1:1	iPrOH	-	RL	Q	12	s.m. + **102**
8	1:1	amylOH	-	RL	Q	12	s.m.
9	1:1	$CHCl_3$	-	RL	P	12	s.m. + **102** + **97**
10	1:1	THF	-	RL	Q	80	c.m. + **97**
11	1:1	$CHCl_3$/MeOH	-	RL	Q	12	s.m. + **103** + **102**
12	1:2	aceton/H_2O	-	RL	P	12	s.m. + **102**
13	1:3	aceton/MeOH	-	RL	P	12	s.m. + **102**
14	1:4	$CHCl_3$/aceton	-	RL	P	12	s.m.
15	2:1	MeOH	-	RL	Q	12	s.m. + **102**
16	3:1	MeOH	-	RL	Q	12	s.m. + **102**
17	1:1	MeOH	a	RL	Q	12	s.m. + **102**
18	1:1	MeOH	a	RL	P	12	s.m. + **102**
19	1:1	MeCN/MeOH	a	RL	Q	12	s.m. + **102**
20	1:1	MeOH	$LiClO_4$	RL	P	12	decomp.
21	1:1	$CHCl_3$	$AlCl_3$	RL	P	12	decomp.
22	1:1	$CHCl_3$	$SnCl_4$	RL	P	12	c.m.
23	1:1	$CHCl_3$	AcOH	RL	P	12	s.m. + **97**
24	1:1	$CHCl_3$	pTSA	RL	P	12	s.m. + **97**

25	1:1	MeOH	-	Hg150	P	rt	s.m. + **102**
26	1:1	MeOH	-	Hg150	P	rt	s.m. + **102**
27	1:1	aceton/H_2O	-	Hg150	P	rt	s.m. + **102**
28	1:1	aceton/MeOH	-	Hg150	P	rt	s.m. + **102**
29	3:1	MeOH	-	Hg150	P	rt	s.m. + **102**
30	1:1	MeOH	-	Hg150	Q	>100	s.m. + **97**
31	3:1	MeCN/H_2O	-	Hg150	Q	>100	s.m. + **97**
32	5:1	$CHCl_3$/MeOH	-	Hg150	Q	rt	s.m. + **102**
33	1:1	MeOH	-	SL300W	Q	4	s.m. + **102**
34	1:1	MeCN/MeOH	-	SL300W	Q	4	s.m. + **102**
35	1:1	MeOH	-	SL300W	P	4	s.m. + **102**
36	1:1	MeCN/MeOH	-	SL300W	P	4	s.m. + **102**
37	1:1	MeOH	a	SL500W	Q	6	s.m. + **102**
38	1:1	MeCN/MeOH	a	SL500W	Q	6	s.m. + **102**
39	1:1	aceton/H_2O	-	SL500W	Q	6	s.m. + **102**
40	1:1	MeOH	a	SL500W	P	6	s.m. + **102**
41	1:1	$CHCl_3$/MeOH	-	SL500W	P	4	s.m. + **102**
42	1:1	MeOH	a	SL750W	Q	4	s.m. + **102**
43	1:1	MeCN/H_2O	-	SL750W	Q	4	s.m. + **102**
44	1:1	MeOH/H_2O	-	SL750W	Q	4	s.m. + **102**
45	1:1	MeOH	-	SL750W	P	4	s.m. + **102**
46	1:1	aceton/H_2O	-	SL750W	P	4	s.m. + **102**
47	1:1	MeOH	-	SL1000W	Q	4	s.m. + **102**
48	1:1	aceton/H_2O	-	SL1000W	Q	4	s.m. + **102**
49	1:1	$CHCl_3$	-	SL1000W	Q	4	s.m. + **102** + **103** + **97**
50	1:1	MeOH	-	SL1000W	P	4	s.m. + **102**
51	1:1	MeCN/MeOH	-	SL1000W	P	4	s.m. + **102**
52	1:1	MeOH	-	RN	P	rt	s.m. + **102**
53	1:1	MeOH/$CHCl_3$	-	RN	P	rt	s.m. + **102**
54	1:1	$CHCl_3$	-	RN	P	rt	s.m. + **102**
55	4:1	Aceton/H_2O	-	RN	P	rt	s.m. + **102**
56	1:4	Aceton/H_2O	-	RN	P	rt	s.m. + **102**
57	1:1	MeOH	-	RN	Q	rt	s.m. + **102**
58	1:1	MeOH	pHb4	RN	Q	rt	s.m. + **97**
59	1:1	MeOH	pHb7	RN	Q	rt	decomp.
60	1:1	MeOH	pHb12	RN	Q	rt	decomp.
61	1:3	$CHCl_3$	-	RN	Q	rt	s.m. + **102**
62	1:1	MeOH	-	Hg450	P	rt	s.m. + **102**
63	1:1	MeOH	pHb4	Hg450	P	rt	s.m. + **97**
64	1:1	Aceton/H_2O	-	Hg450	P	rt	s.m. + **102**
65	1:1	MeCN/MeOH	-	Hg450	P	rt	s.m. + **102**
66	1:1	$CHCl_3$	-	Hg450	P	rt	s.m. + **102** + **97**
67	1:1	CH_2Cl_2	-	Hg450	P	rt	s.m. + **102** + **97**
68	1:1	MeOH	-	Hg450	Q	rt	s.m. + **102**
69	1:1	MeCN/MeCN	-	Hg450	Q	rt	s.m. + **102**
70	1:1	aceton/MeOH	-	Hg450	Q	rt	s.m. + **102**
71	1:1	THF	-	Hg450	Q	rt	decomp.

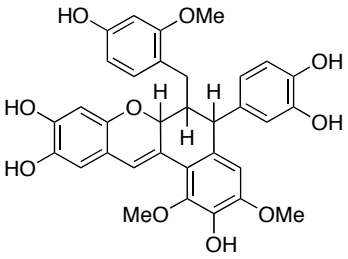
72	1:1	$CHCl_3$	-	Hg450	Q	rt	s.m. + **102** + **97**
73	2:1	MeOH	-	Hg450	Q	rt	s.m. + **102**
74	4:1	MeOH	-	Hg450	Q	rt	s.m. + **102**
75	7:1	MeOH	-	Hg450	Q	rt	s.m. + **102**
76	10:1	MeOH	-	Hg450	Q	rt	s.m. + **103** + **102** + **97**

RL = reptile sun lamp, 275 W; Hg150 = Mercury medium pressure lamp, 150 W; Hg450 = Mercury medium pressure lamp, 450 W; SLXXW = stationary lamp, flexible W (300 W – 1000 W); RN = Rayonet, 250 W; a = phenylboronic acid; pHbXX = pH buffer XX (4 – 12); P = pyrex filter; Q = quartz filter; s.m. = starting material; c.m. = complex mixture; decomp. = decomposition.

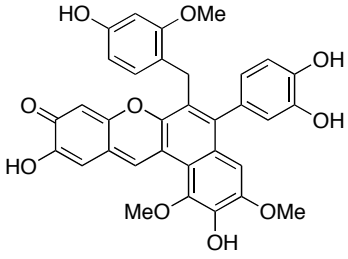
Observed side-products:



102



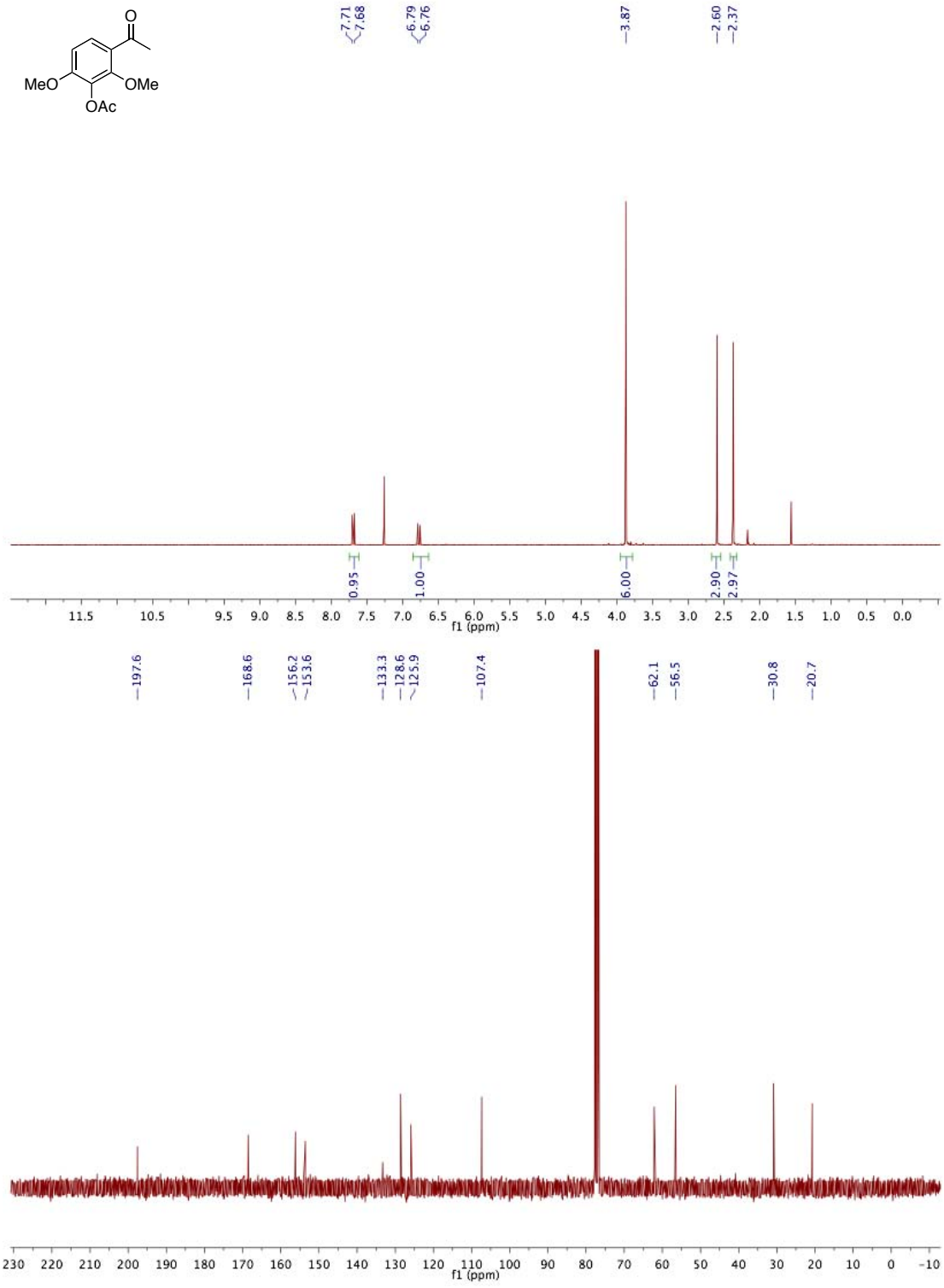
103

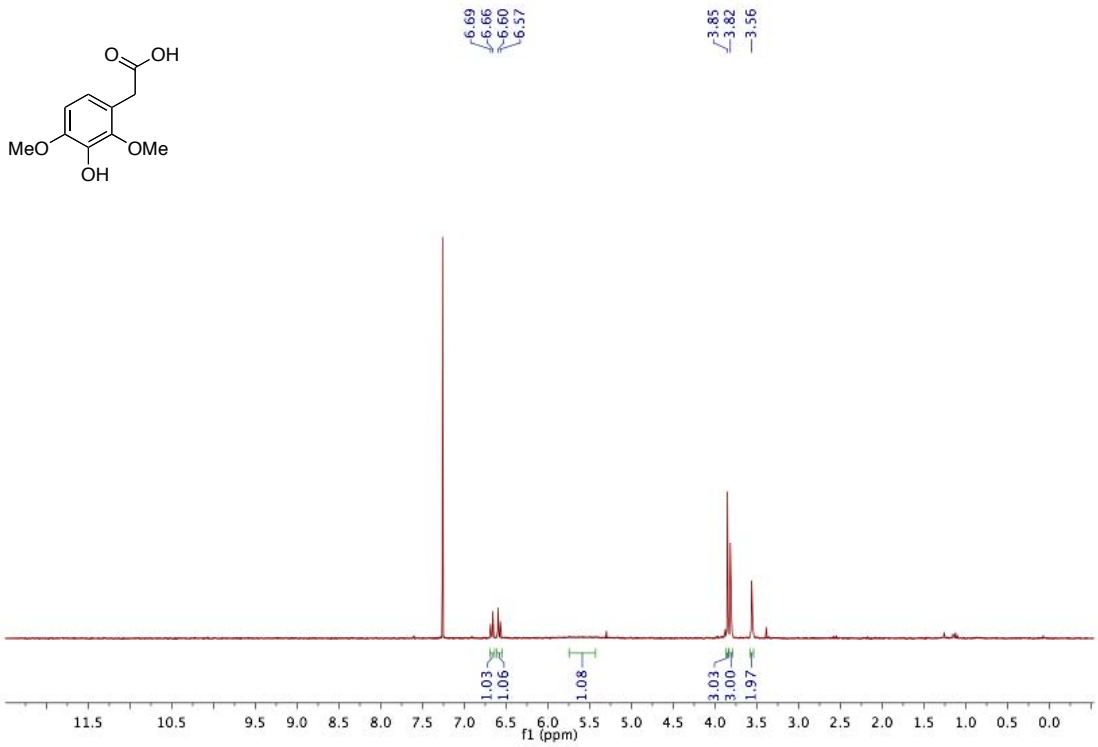


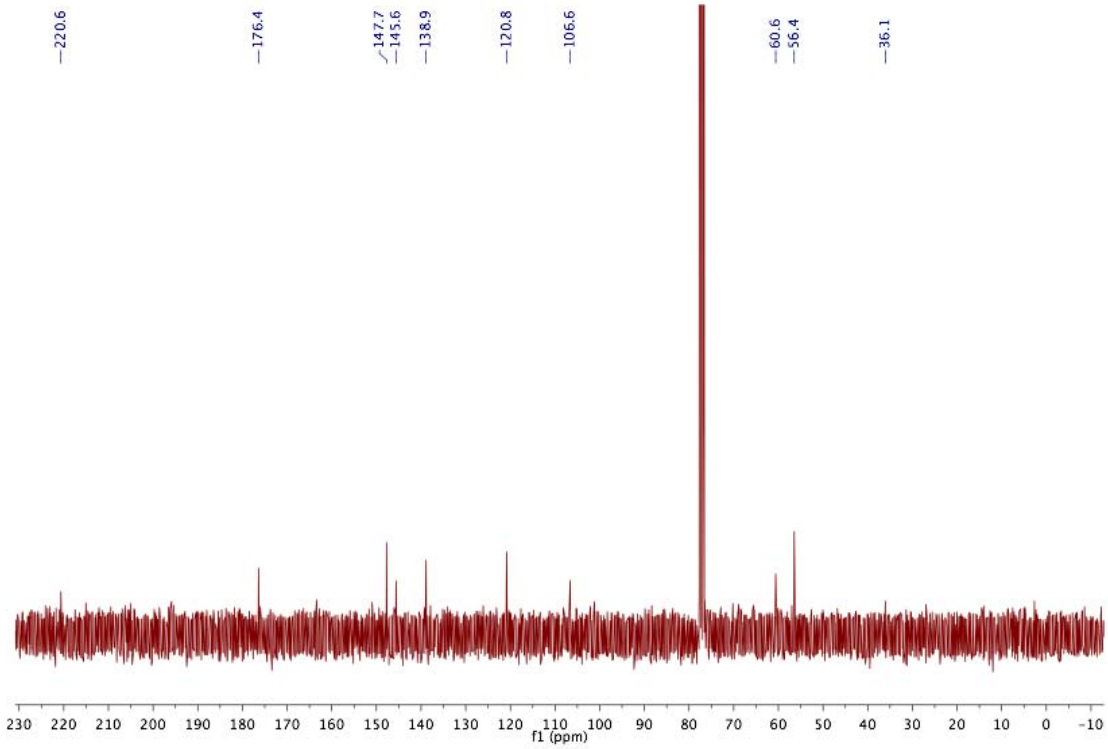
97

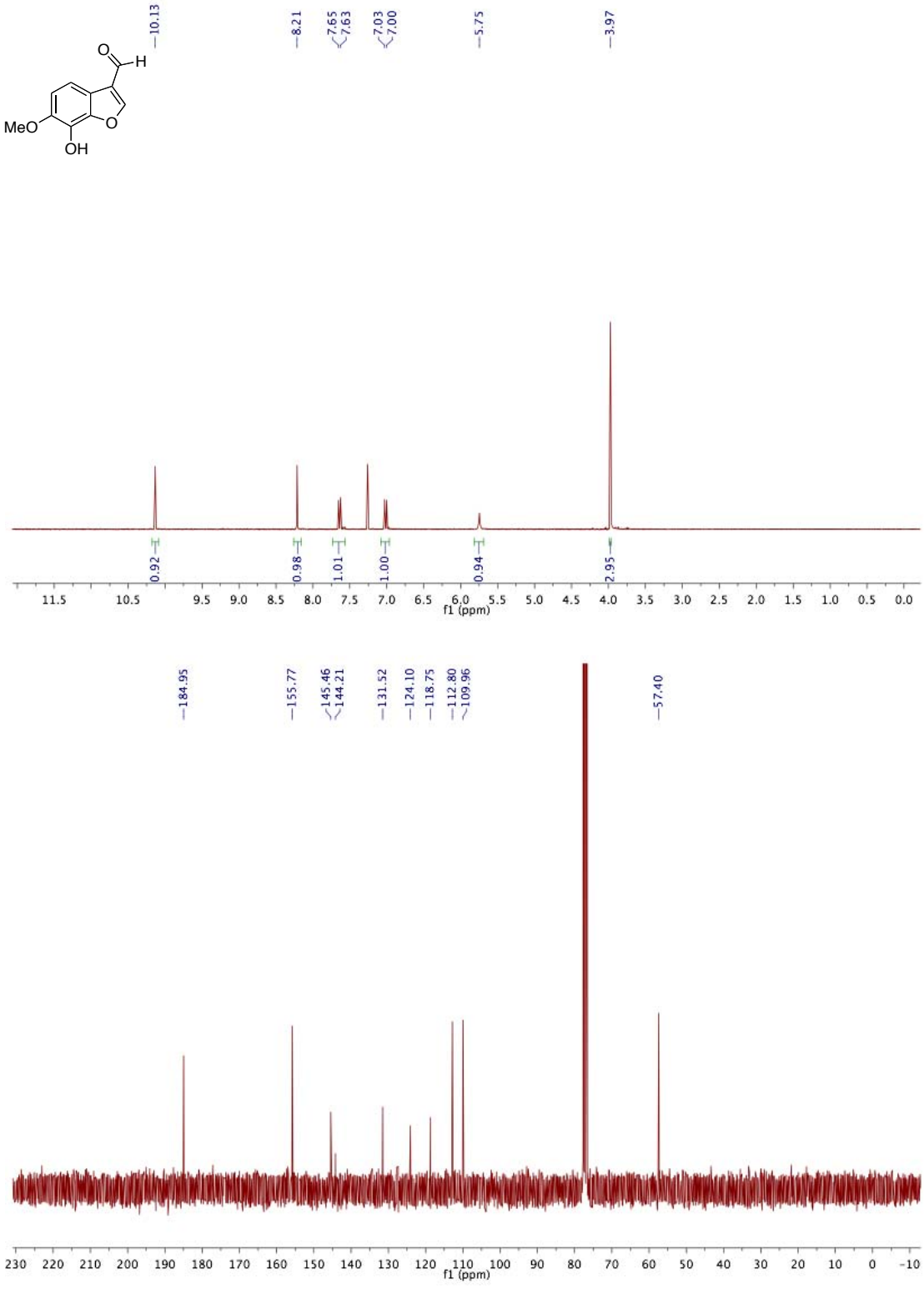
Formation of **102** in case of protic solvent (*R* = H, Me, Et, *i*Pr). Isolation of **102** was not possible, but was detected by crude NMR. Formation of **103** could be detected by HR-MS and ^{1}H NMR (^{13}C NMR showed formation of oxidized product **97**).

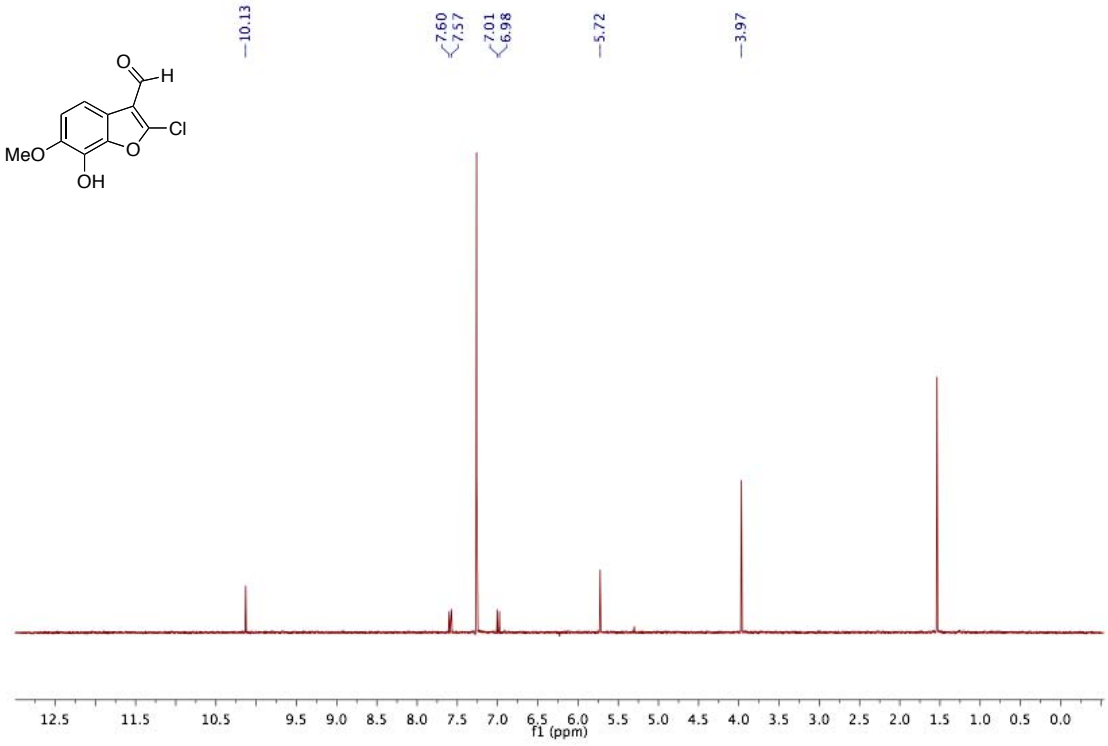
VII. Appendix II – Spectral Data

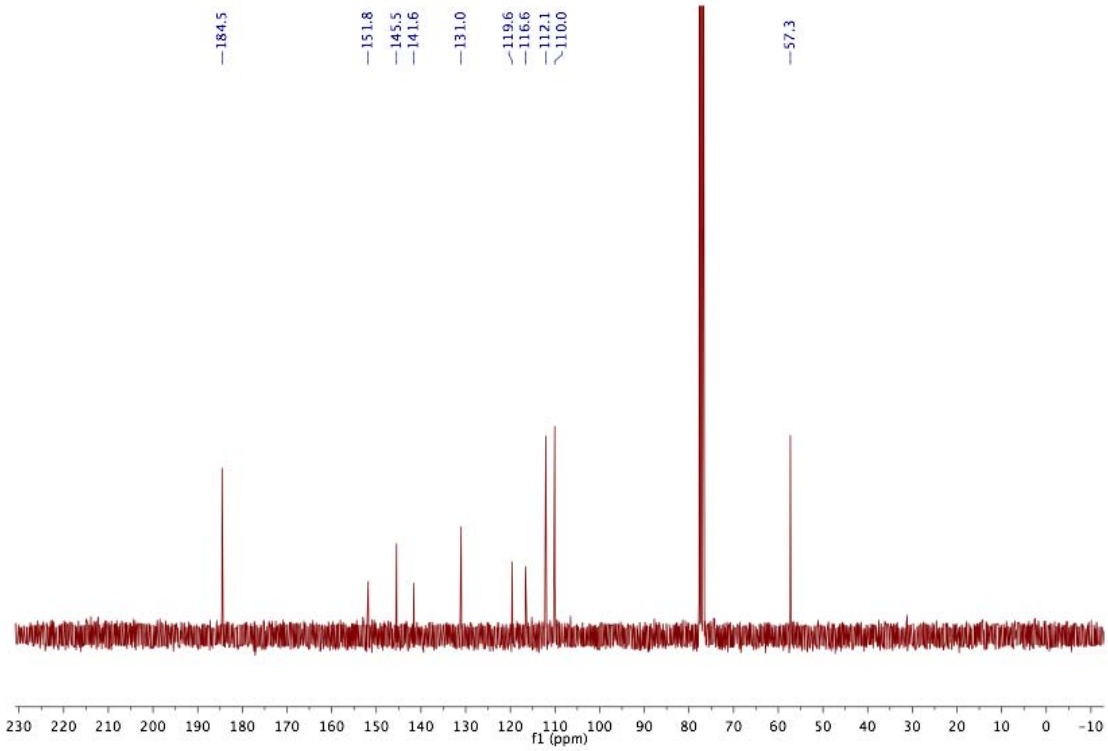


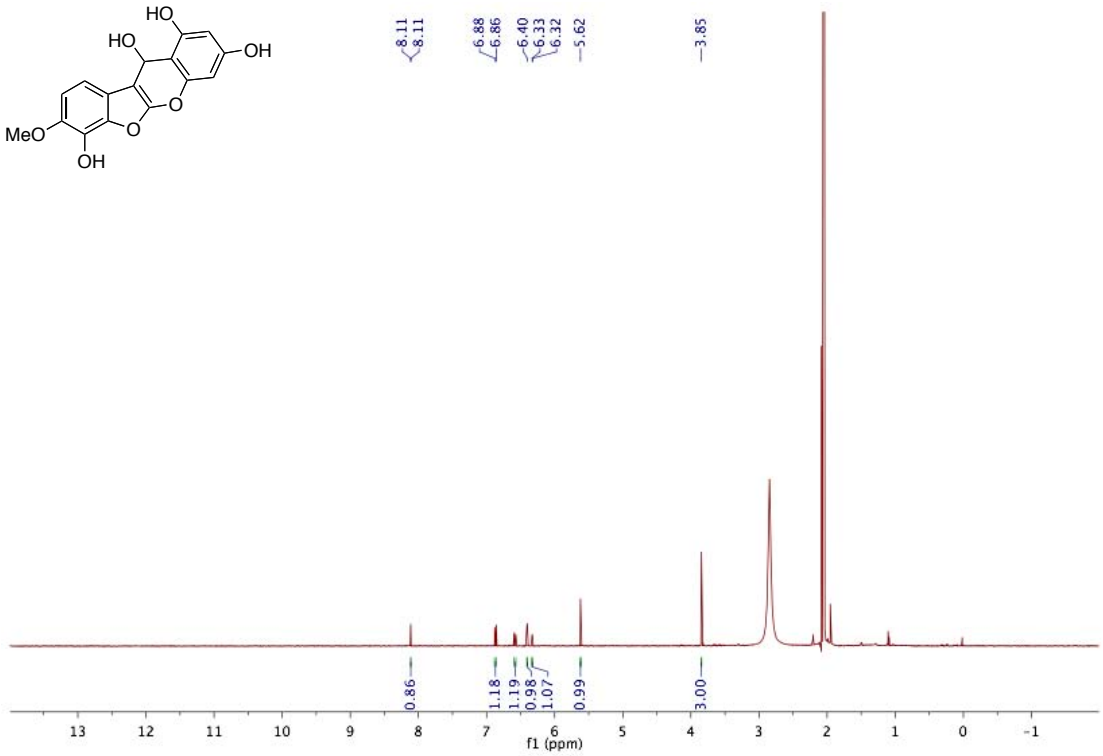

O
OH
MeO
OMe
OH
6.69
6.66
6.60
6.57
3.85
3.82
3.56
1.03
1.06
1.08
3.03
3.00
1.97
f1 (ppm)

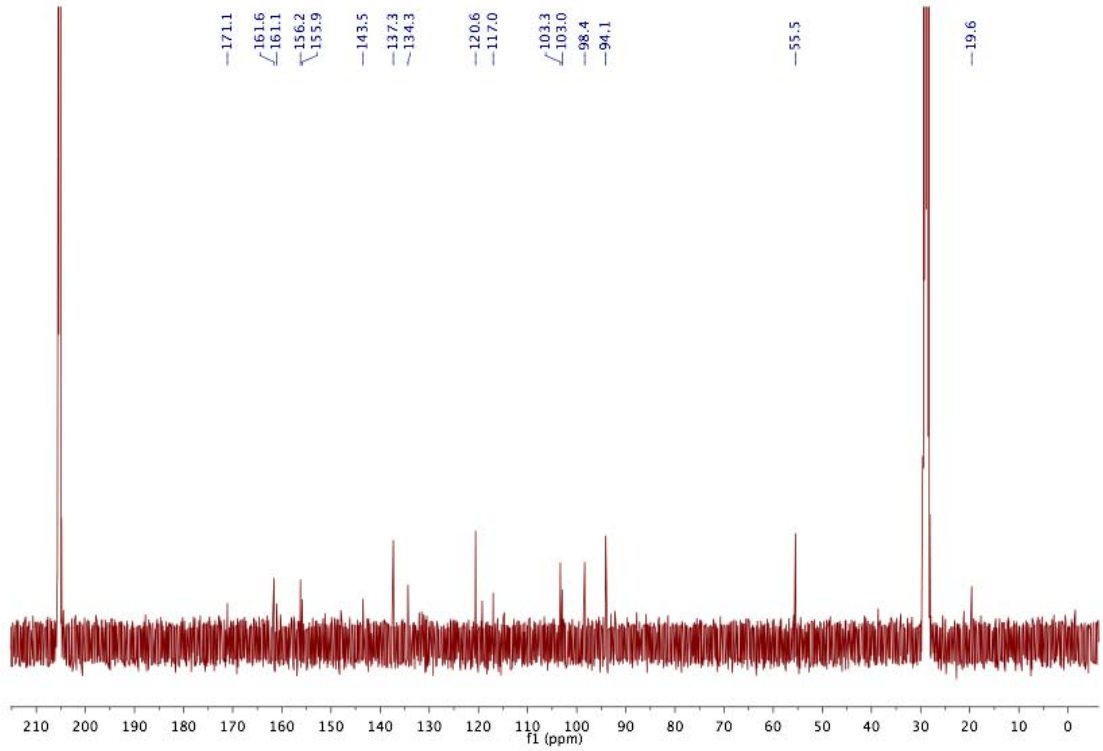

220.6
176.4
147.7
145.6
138.9
120.8
106.6
60.6
56.4
36.1
f1 (ppm)

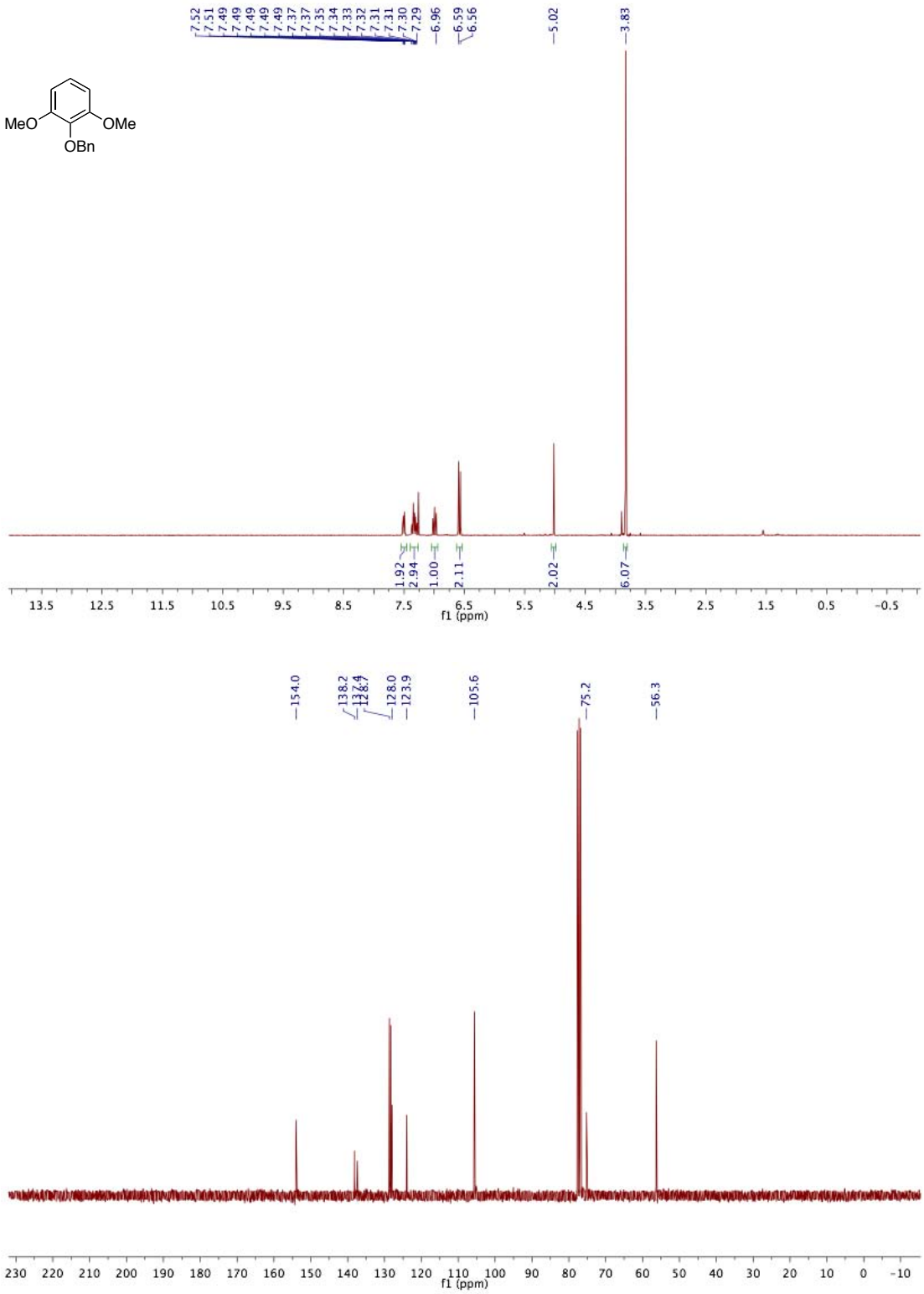

10.13
8.21
7.65
7.63
7.03
7.00
5.75
3.97
O
H
MeO
OH
0.92
0.98
1.01
1.00
0.94
2.95
f1 (ppm)
184.95
155.77
145.46
144.21
131.52
124.10
118.75
112.80
109.96
57.40
f1 (ppm)

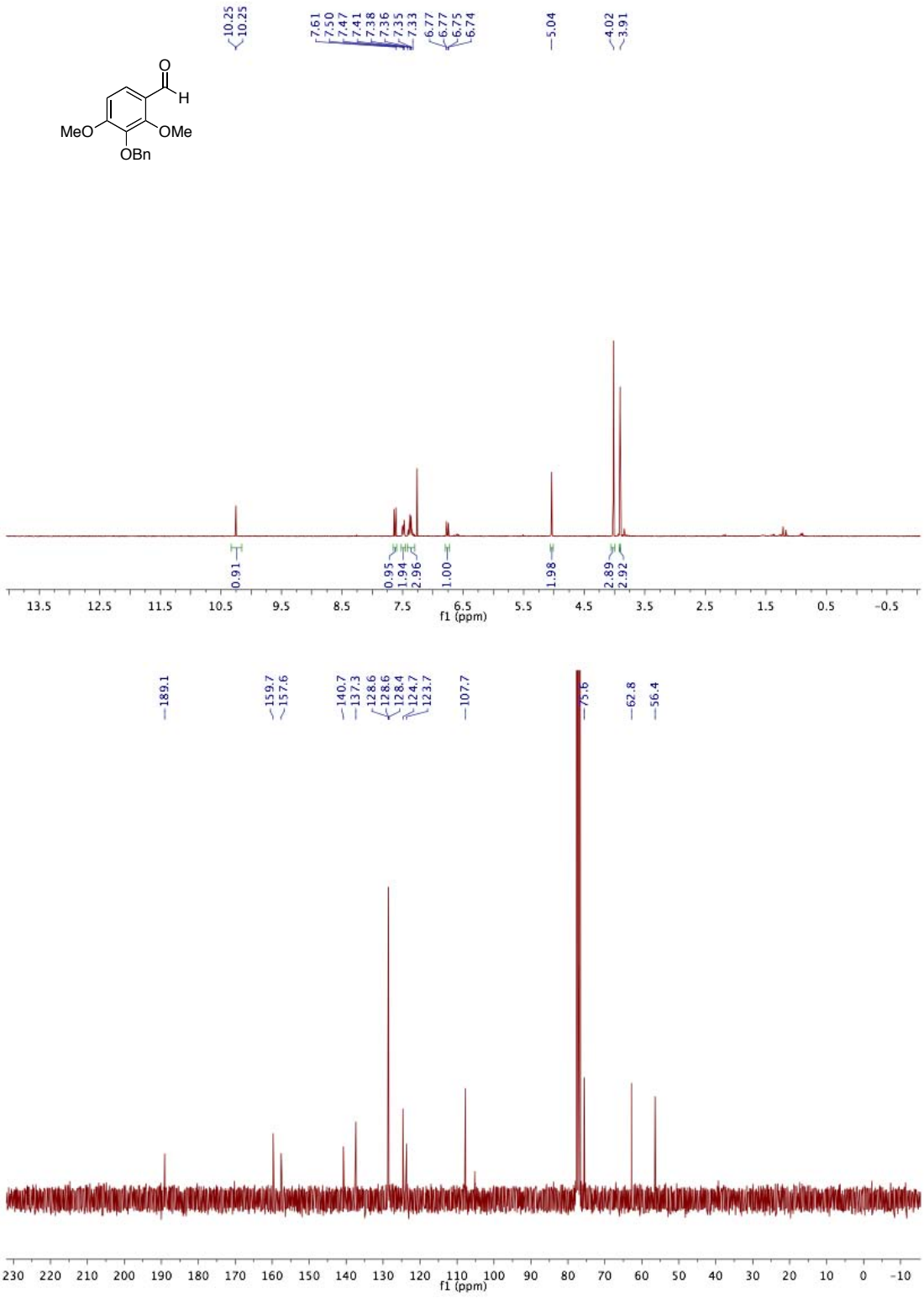

O
H
Cl
MeO
O
OH
10.13
7.60
7.57
7.01
6.98
5.72
3.97
12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

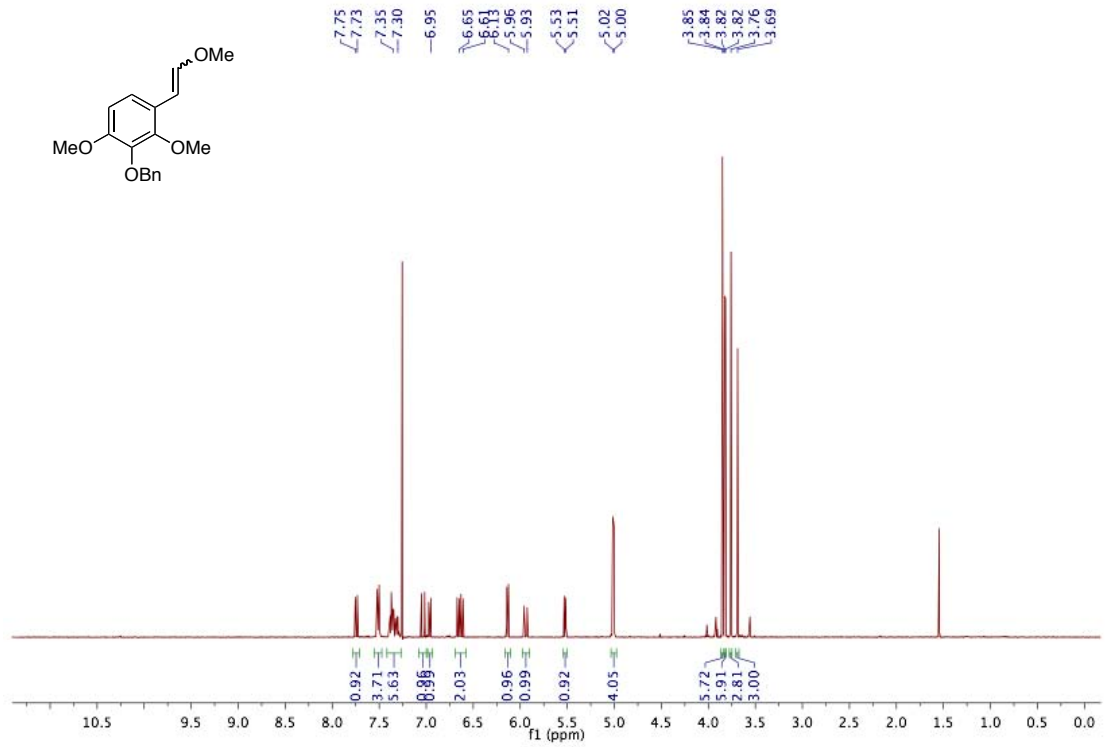

184.5
151.8
145.5
141.6
131.0
119.6
116.6
112.1
110.0
57.3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

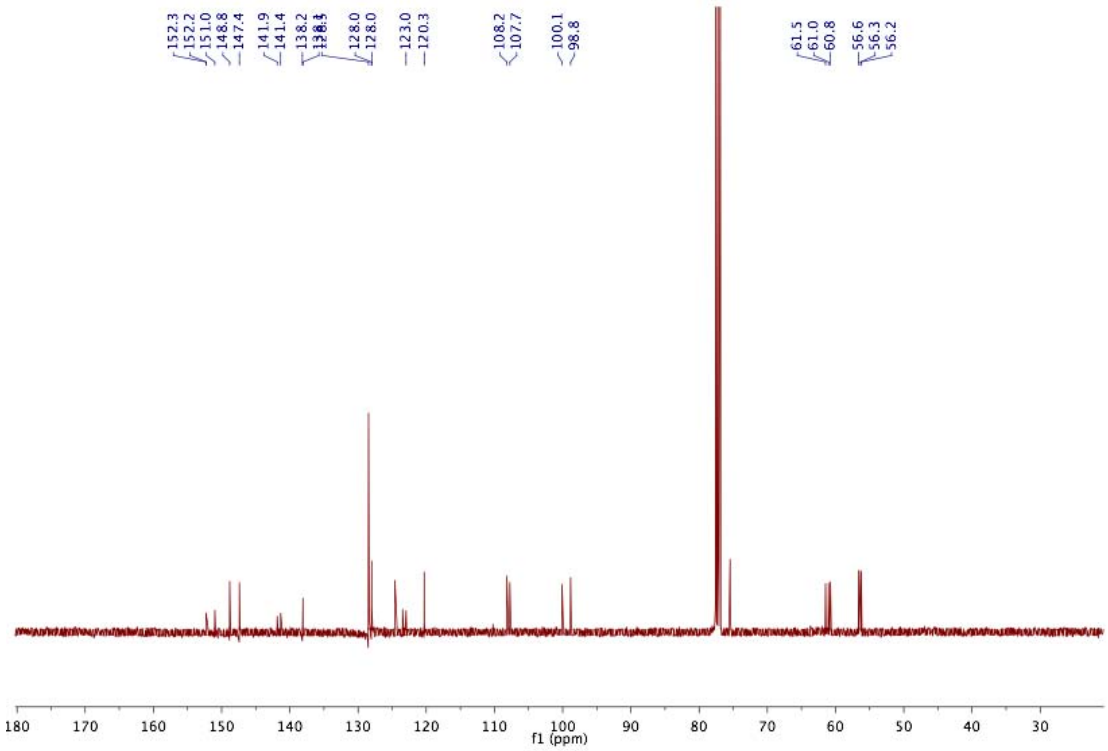

HO
HO
OH
MeO
O
O
OH
8.11
8.11
6.88
6.86
6.40
6.33
6.32
5.62
3.85
0.86
1.18
1.19
0.98
1.07
0.99
3.00
f1 (ppm)

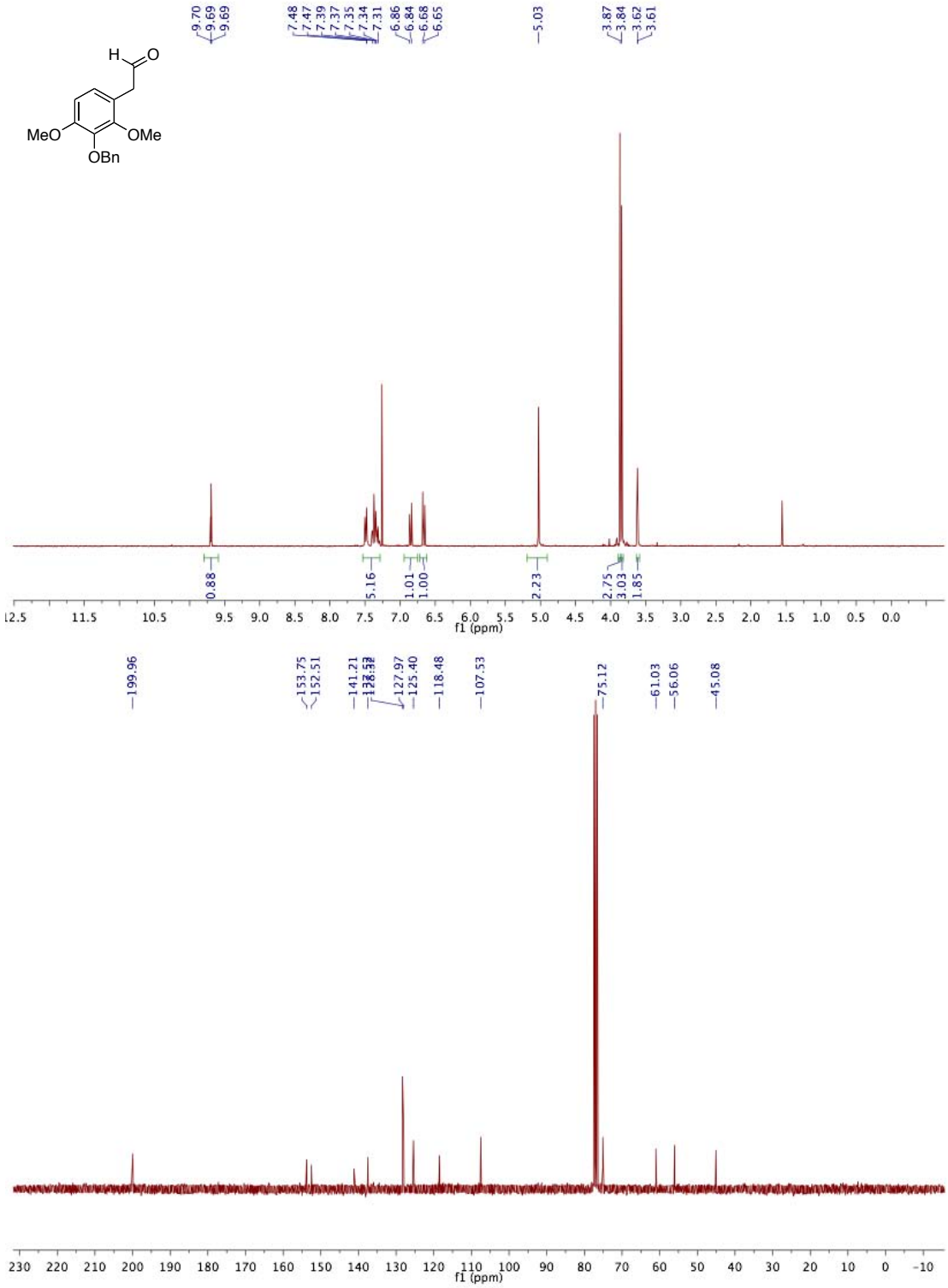

171.1
161.6
161.1
156.2
155.9
143.5
137.3
134.3
120.6
117.0
103.3
103.0
98.4
94.1
55.5
19.6
f1 (ppm)

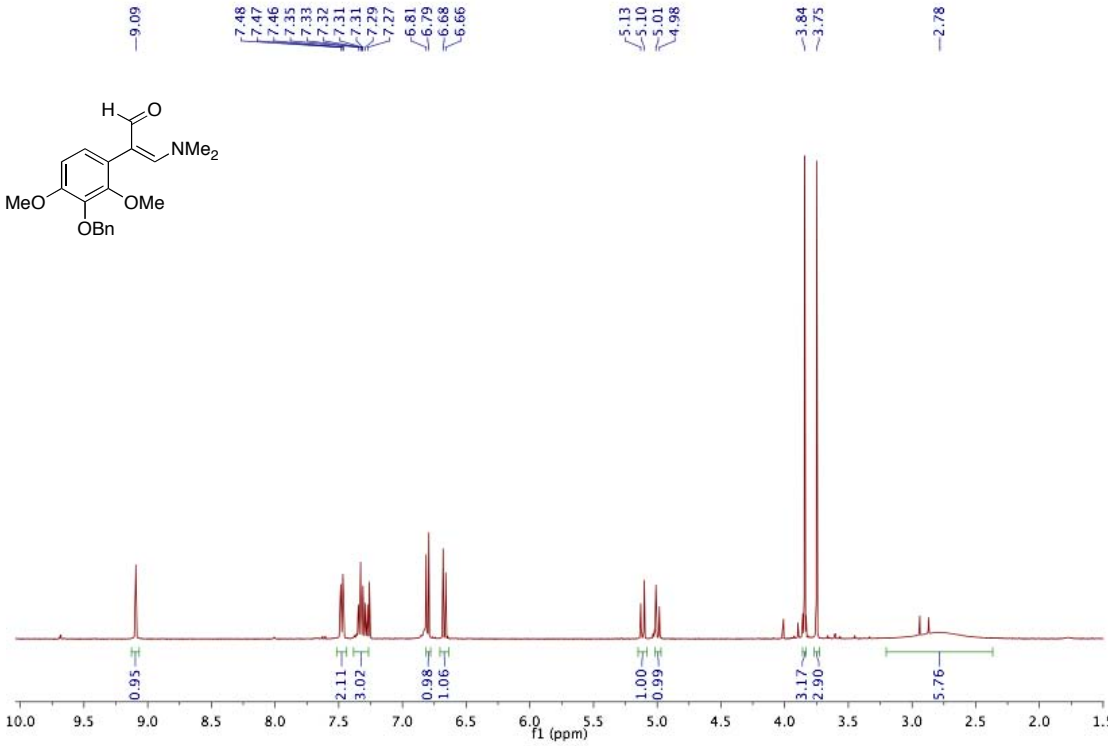

MeO
OMe
OBn
7.52
7.51
7.49
7.49
7.49
7.49
7.49
7.37
7.37
7.35
7.34
7.33
7.32
7.31
7.31
7.30
7.29
6.96
6.59
6.56
5.02
3.83
1.92
2.94
1.00
2.11
2.02
6.07
f1 (ppm)
154.0
138.2
137.4
128.7
128.0
123.9
105.6
75.2
56.3
f1 (ppm)

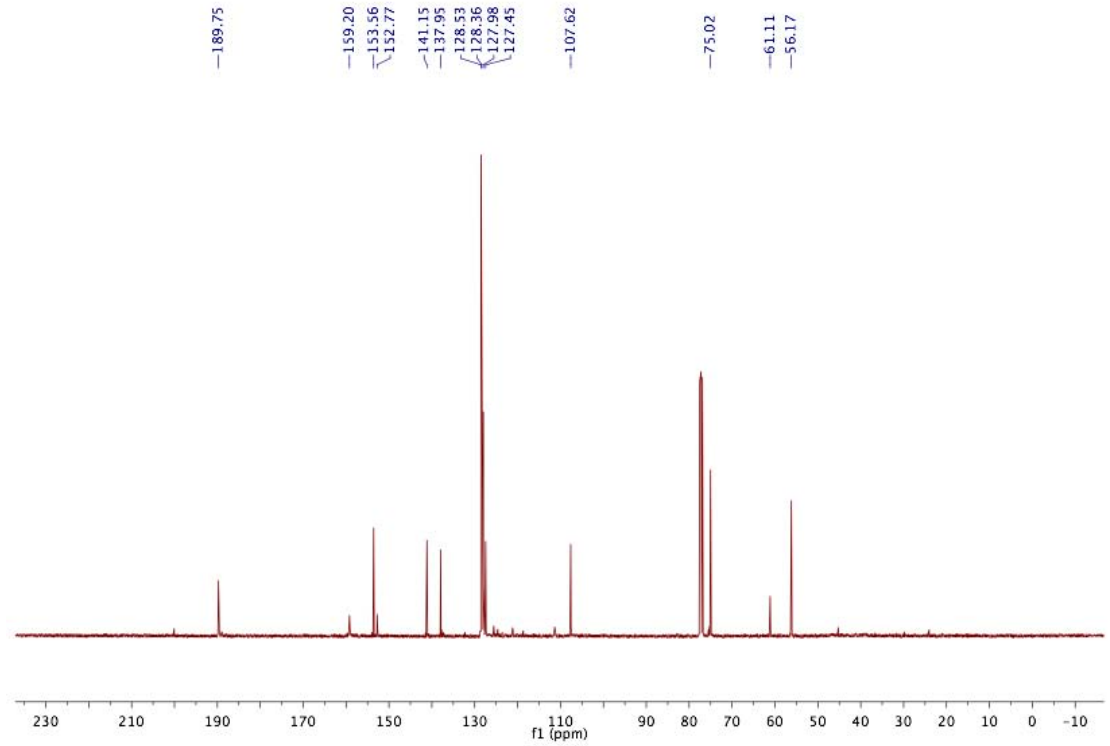

10.25
10.25
7.61
7.50
7.47
7.41
7.38
7.36
7.35
7.33
6.77
6.77
6.75
6.74
5.04
4.02
3.91
O
H
MeO
OMe
OBn
0.91
0.95
1.94
2.96
1.00
1.98
2.89
2.92
f1 (ppm)
189.1
159.7
157.6
140.7
137.3
128.6
128.6
128.4
124.7
123.7
107.7
75.6
62.8
56.4
f1 (ppm)

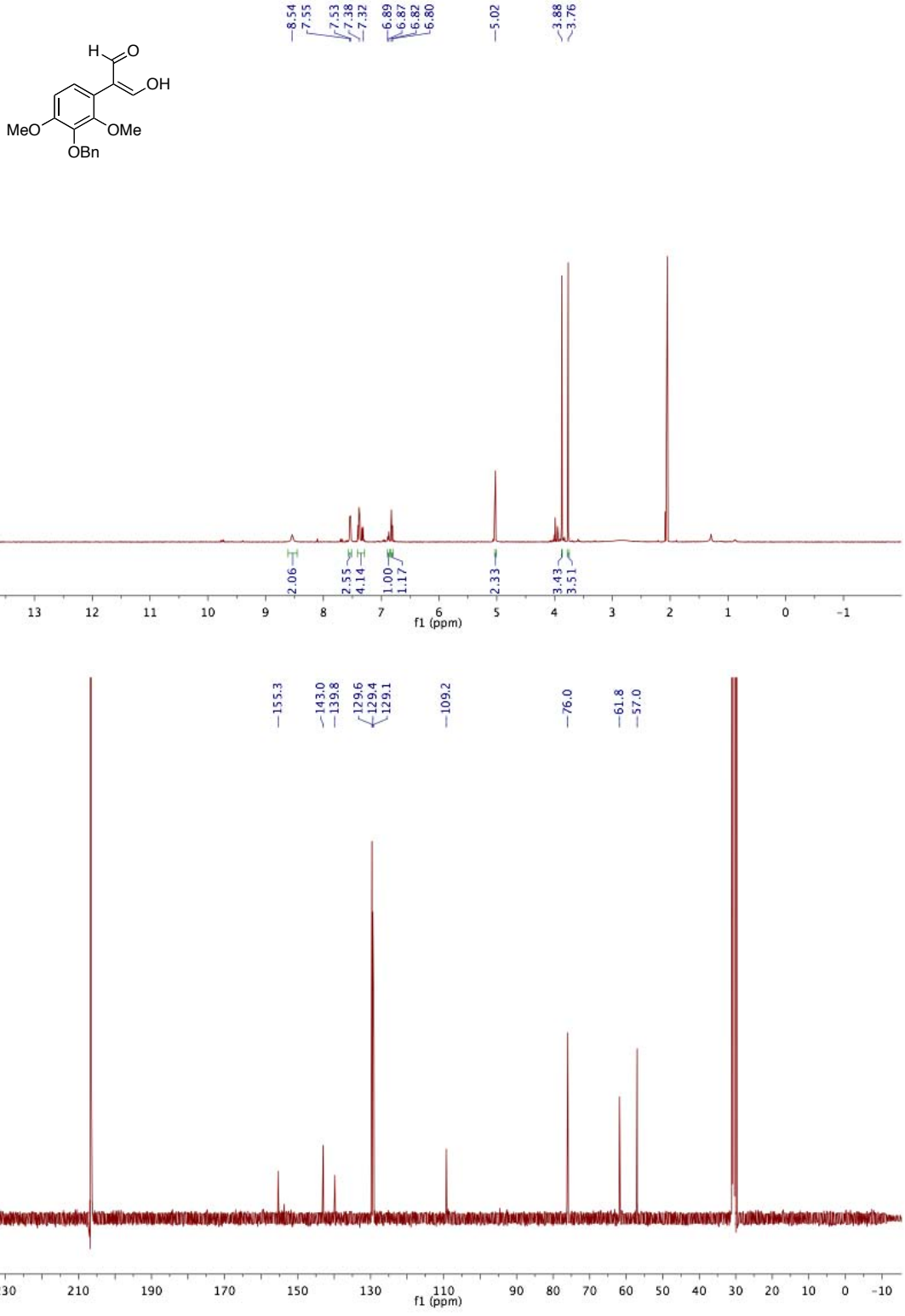

OMe
MeO
OMe
OBn
7.75
7.73
7.35
7.30
6.95
6.65
6.61
6.13
5.96
5.93
5.53
5.51
5.02
5.00
3.85
3.84
3.82
3.82
3.76
3.69
0.92
3.71
5.63
2.03
0.96
0.99
0.92
4.05
5.72
5.91
2.81
3.00
f1 (ppm)

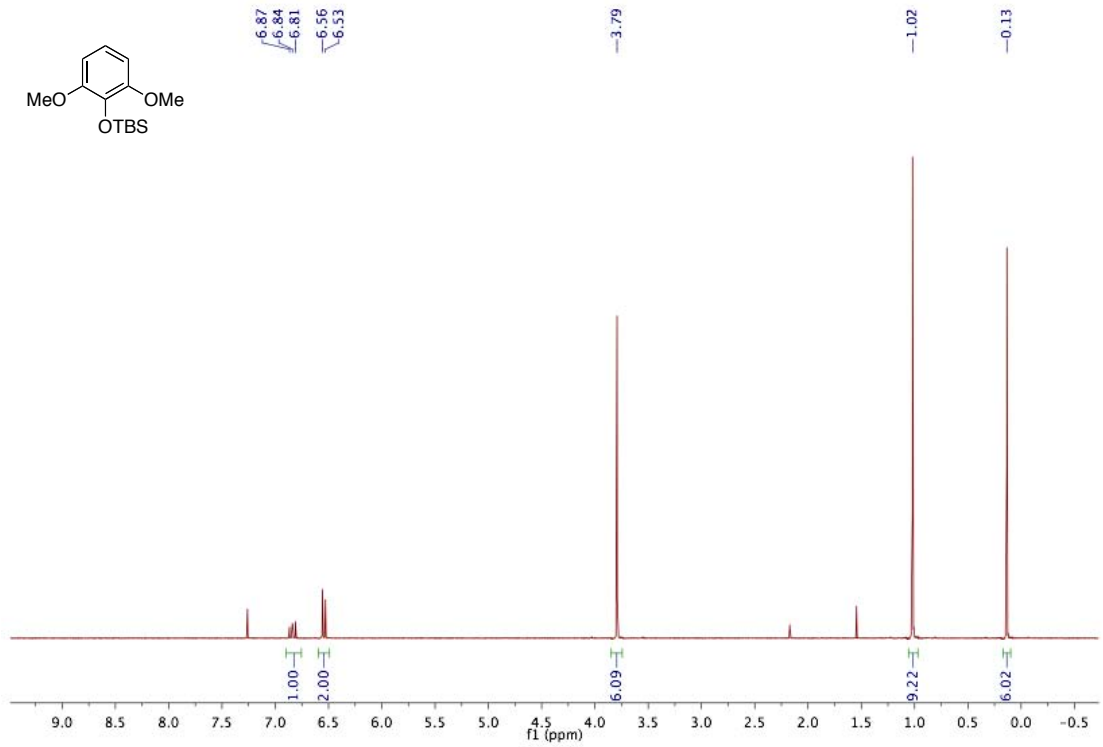

152.3
152.2
151.0
148.8
147.4
141.9
141.4
138.2
128.0
128.0
123.0
120.3
108.2
107.7
100.1
98.8
61.5
61.0
60.8
56.6
56.3
56.2
f1 (ppm)

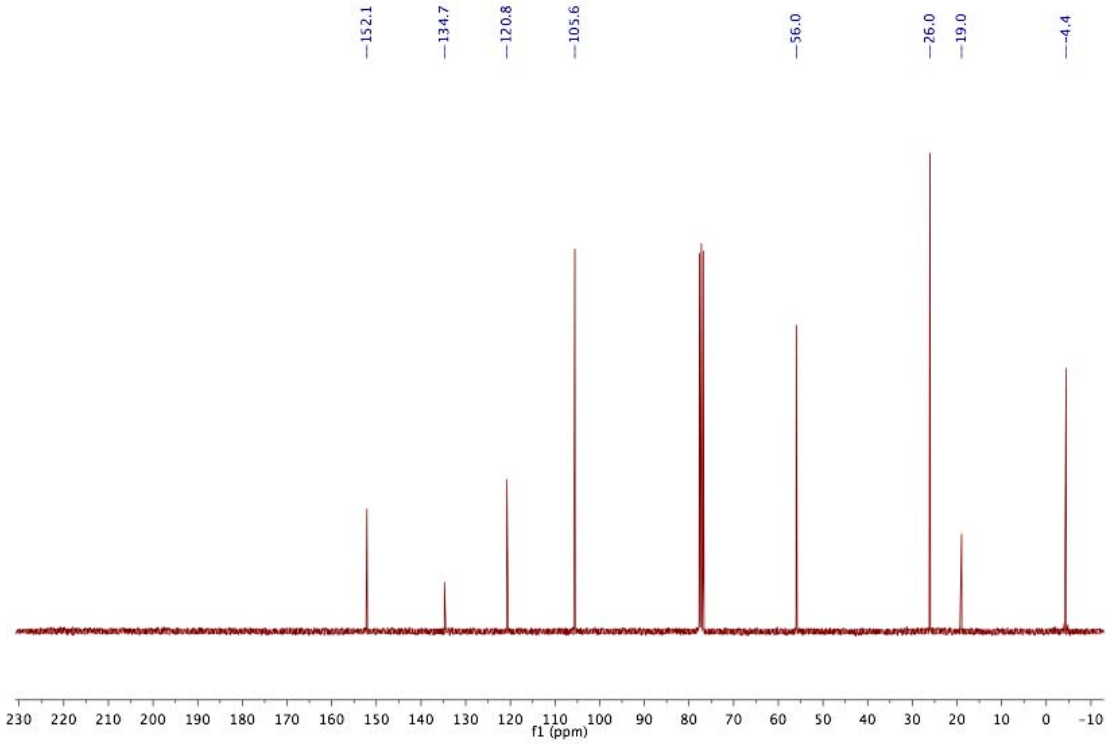

9.70
9.69
9.69
7.48
7.47
7.39
7.37
7.35
7.34
7.31
6.86
6.84
6.68
6.65
5.03
3.87
3.84
3.62
3.61
H
O
MeO
OMe
OBn
0.88
5.16
1.01
1.00
2.23
2.75
3.03
1.85
f1 (ppm)
199.96
153.75
152.51
141.21
127.97
125.40
118.48
107.53
75.12
61.03
56.06
45.08
f1 (ppm)

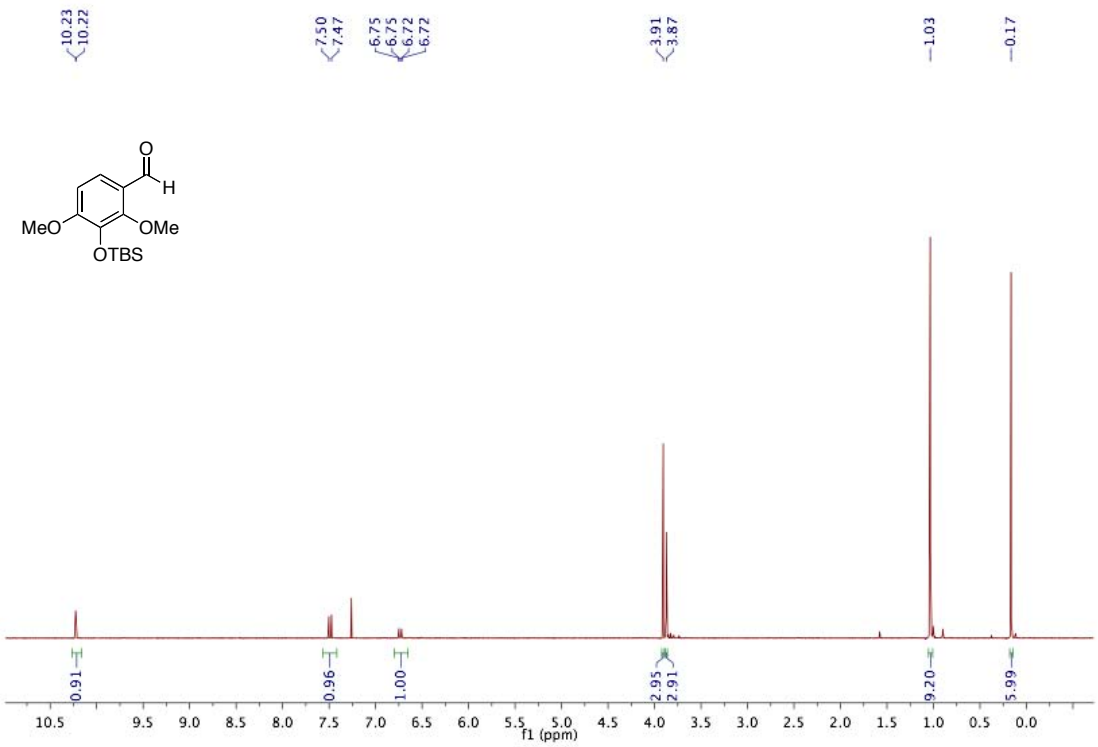

9.09
7.48
7.47
7.46
7.35
7.33
7.32
7.31
7.31
7.29
7.27
6.81
6.79
6.68
6.66
5.13
5.10
5.01
4.98
3.84
3.75
2.78
H
O
NMe2
MeO
OMe
OBn
0.95
2.11
3.02
0.98
1.06
1.00
0.99
3.17
2.90
5.76
f1 (ppm)

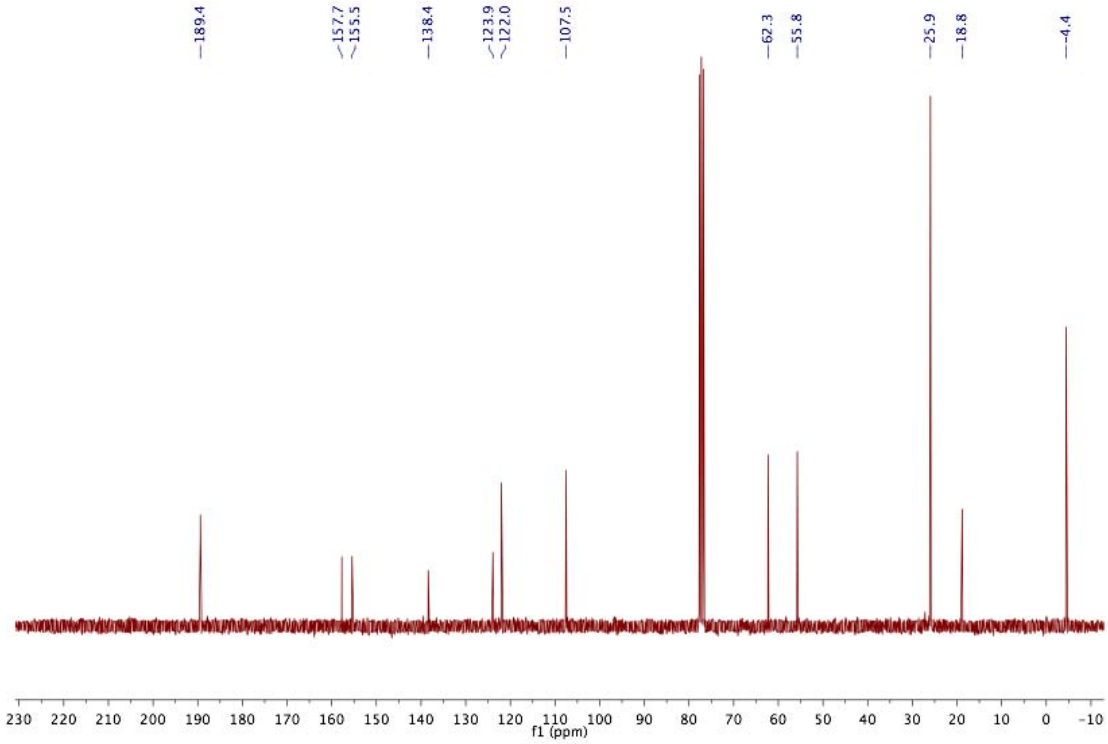

189.75
159.20
153.56
152.77
141.15
137.95
128.53
128.36
127.98
127.45
107.62
75.02
61.11
56.17
f1 (ppm)

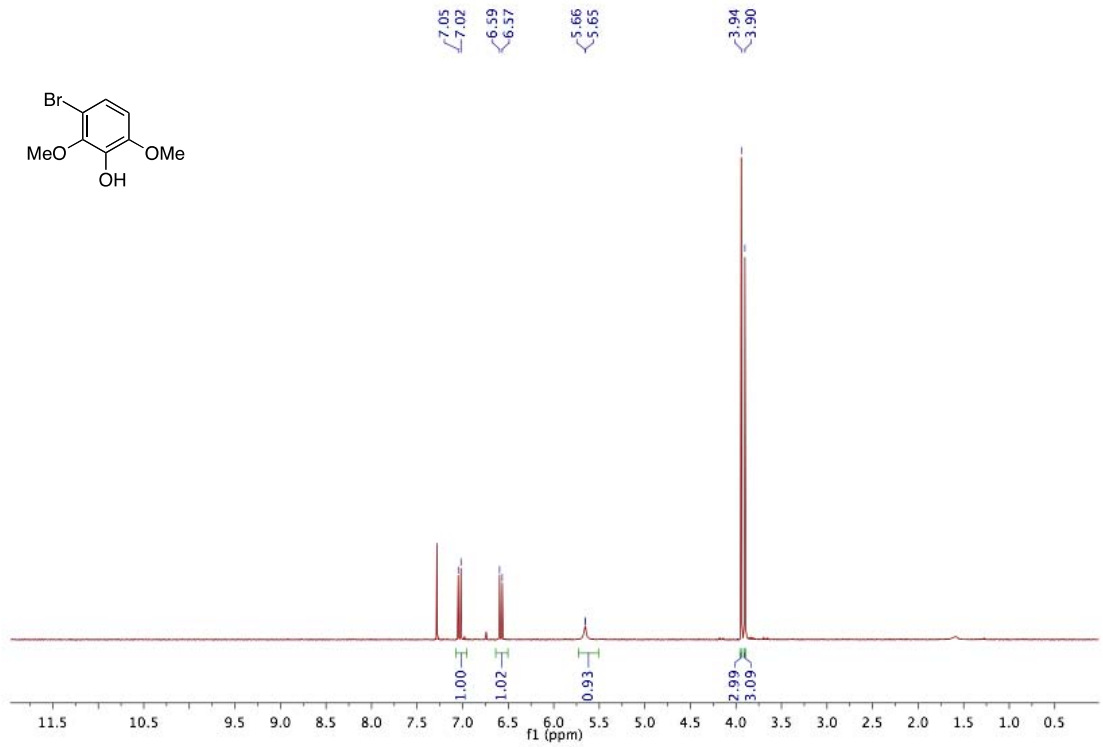

8.54
7.55
7.53
7.38
7.32
6.89
6.87
6.82
6.80
5.02
3.88
3.76
H
O
OH
MeO
OMe
OBn
2.06
2.55
4.14
1.00
1.17
2.33
3.43
3.51
f1 (ppm)
155.3
143.0
139.8
129.6
129.4
129.1
109.2
76.0
61.8
57.0
f1 (ppm)

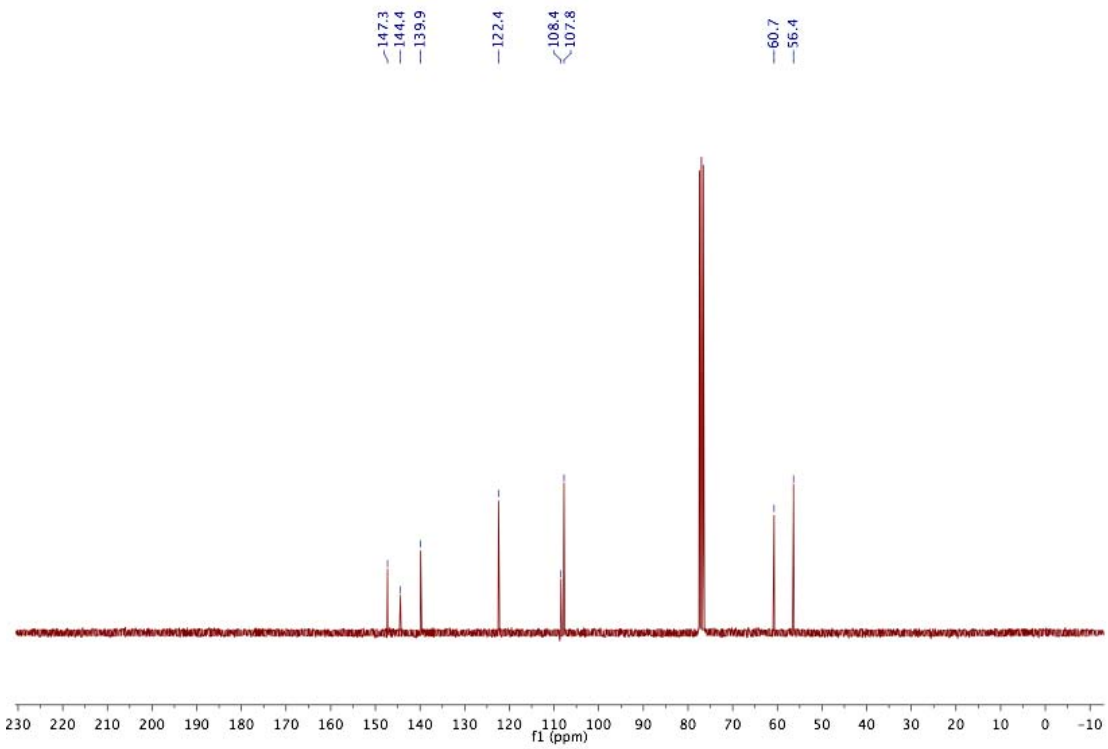

MeO
OMe
OTBS
6.87
6.84
6.81
6.56
6.53
3.79
1.02
0.13
1.00
2.00
6.09
9.22
6.02
f1 (ppm)

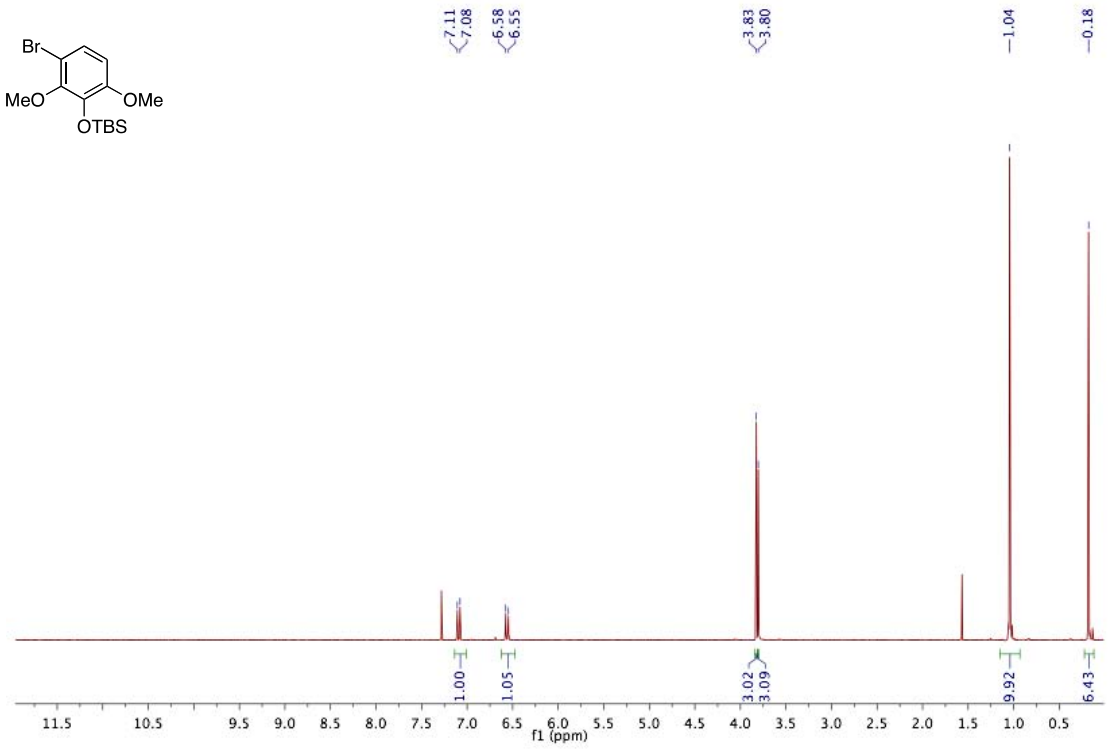

152.1
134.7
120.8
105.6
56.0
26.0
19.0
-4.4
f1 (ppm)

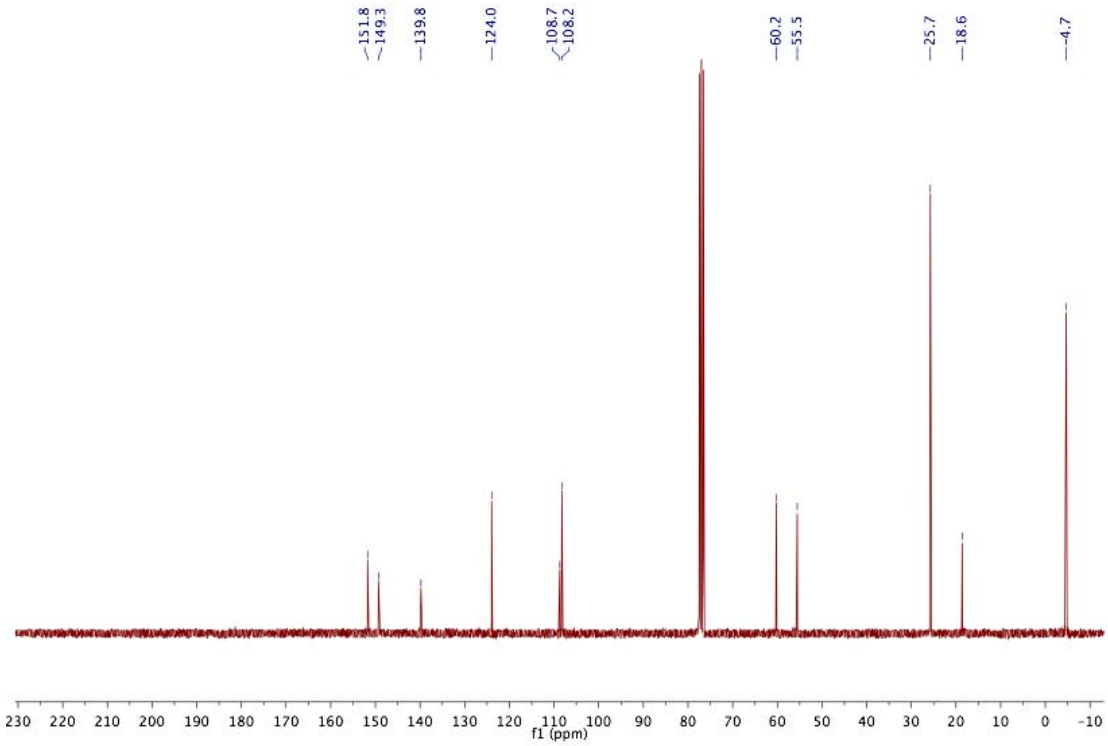

10.23
10.22
7.50
7.47
6.75
6.75
6.72
6.72
3.91
3.87
1.03
0.17
O
H
MeO
OMe
OTBS
0.91
0.96
1.00
2.95
2.91
9.20
5.99
f1 (ppm)

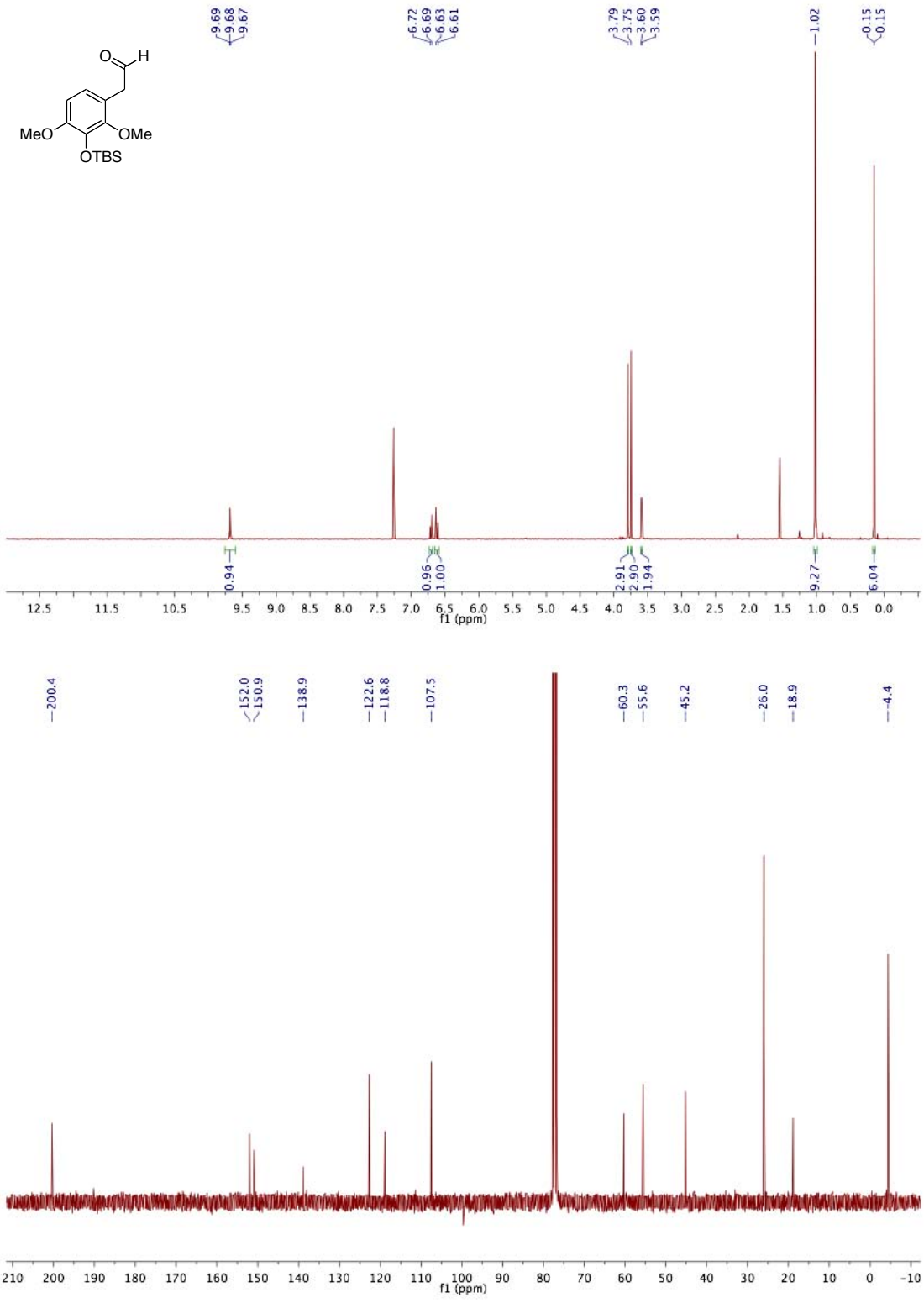

189.4
157.7
155.5
138.4
123.9
122.0
107.5
62.3
55.8
25.9
18.8
-4.4
f1 (ppm)

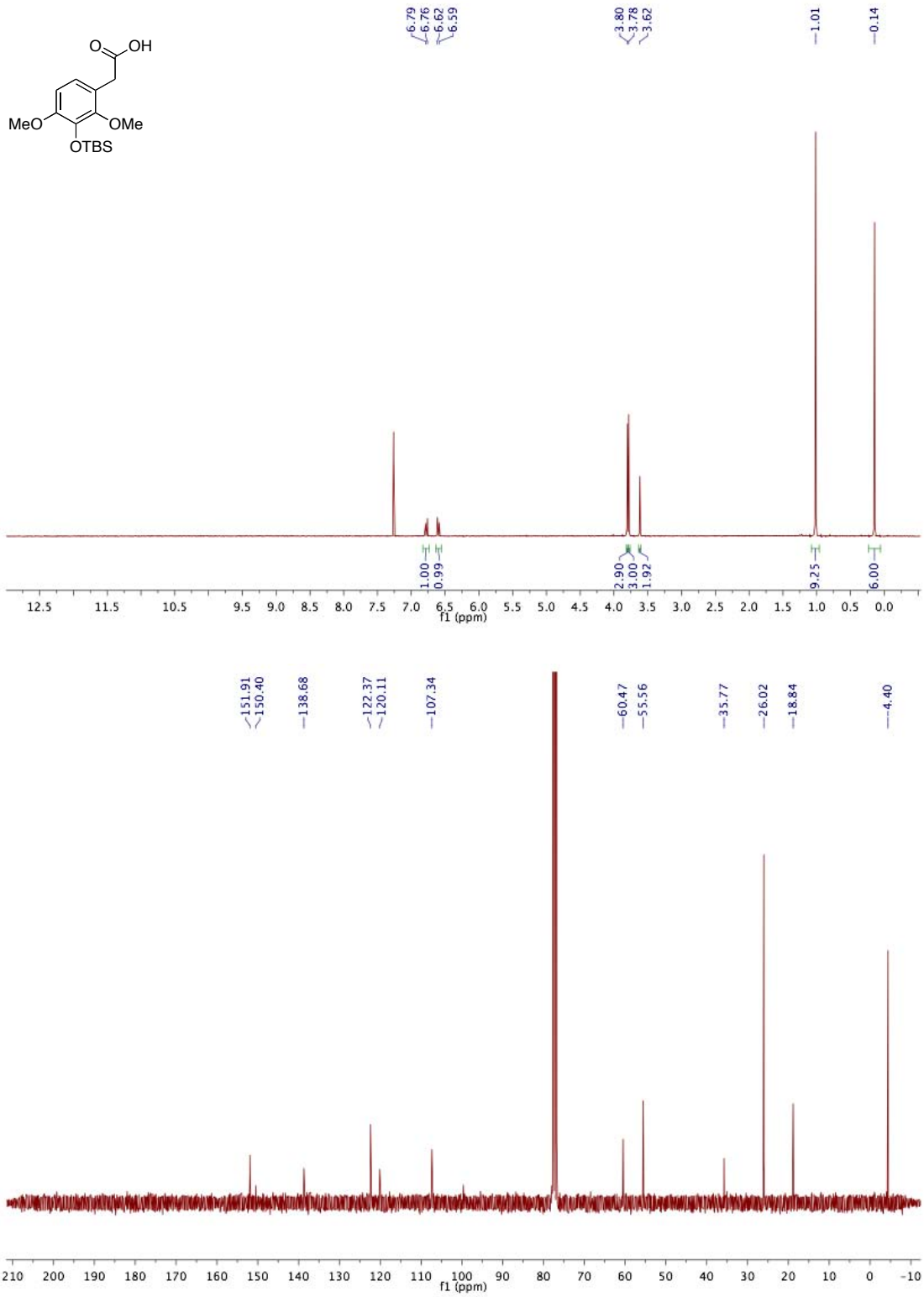

Br
MeO
OMe
OH
7.05
7.02
6.59
6.57
5.66
5.65
3.94
3.90
1.00
1.02
0.93
2.99
3.09
f1 (ppm)

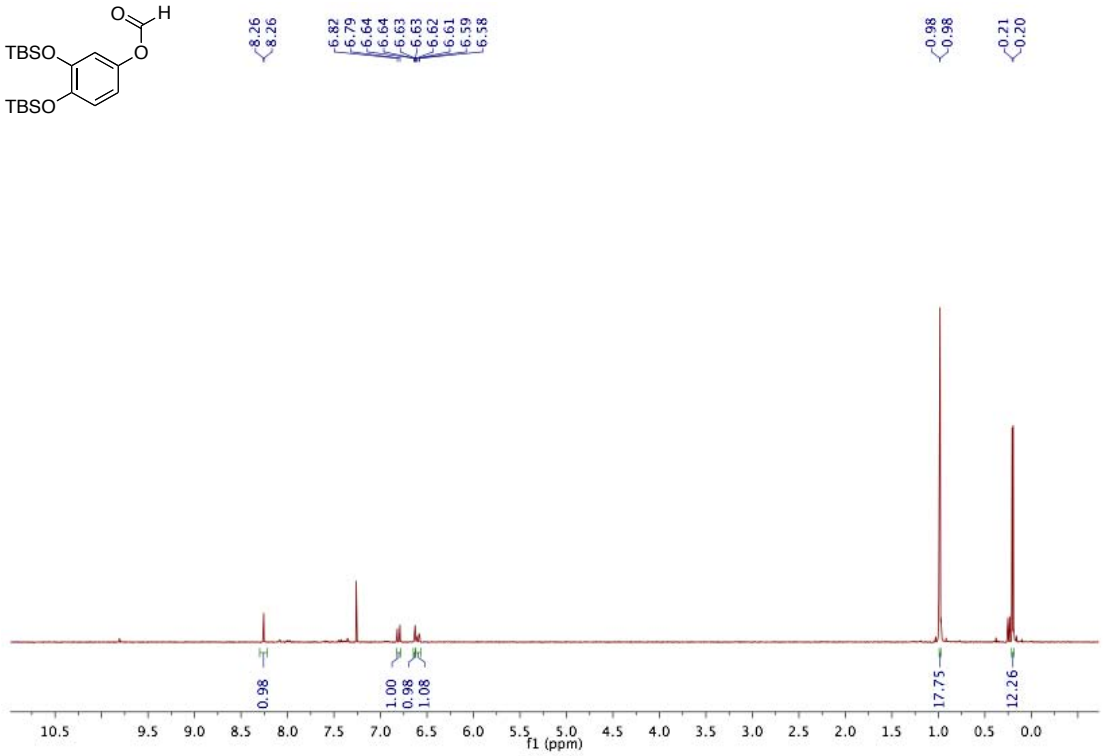

147.3
144.4
139.9
122.4
108.4
107.8
60.7
56.4
f1 (ppm)

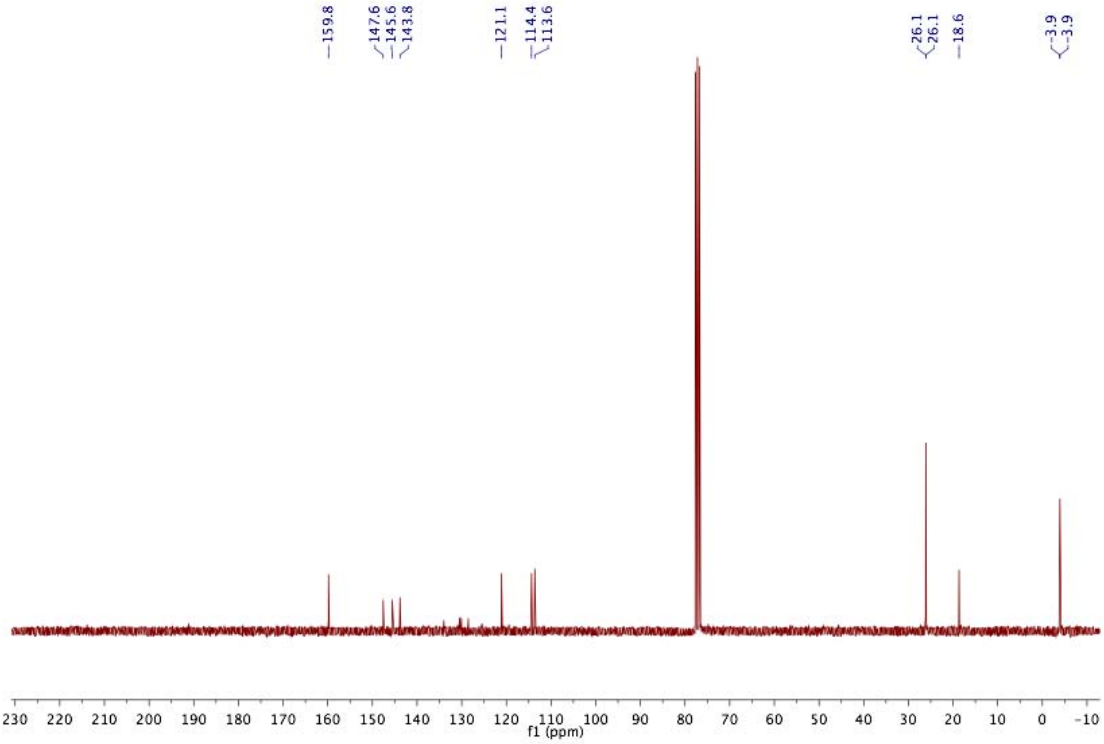

Br
MeO
OMe
OTBS
7.11
7.08
6.58
6.55
3.83
3.80
1.04
0.18
1.00
1.05
3.02
3.09
9.92
6.43
f1 (ppm)

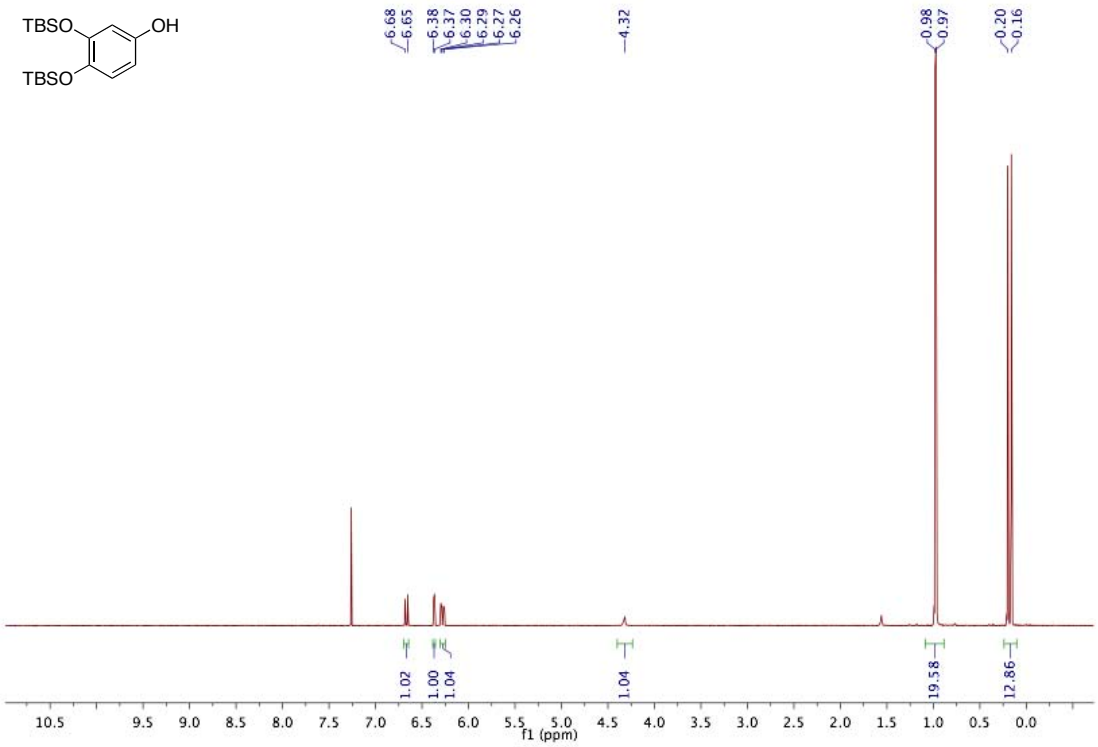

151.8
149.3
139.8
124.0
108.7
108.2
60.2
55.5
25.7
18.6
4.7
f1 (ppm)

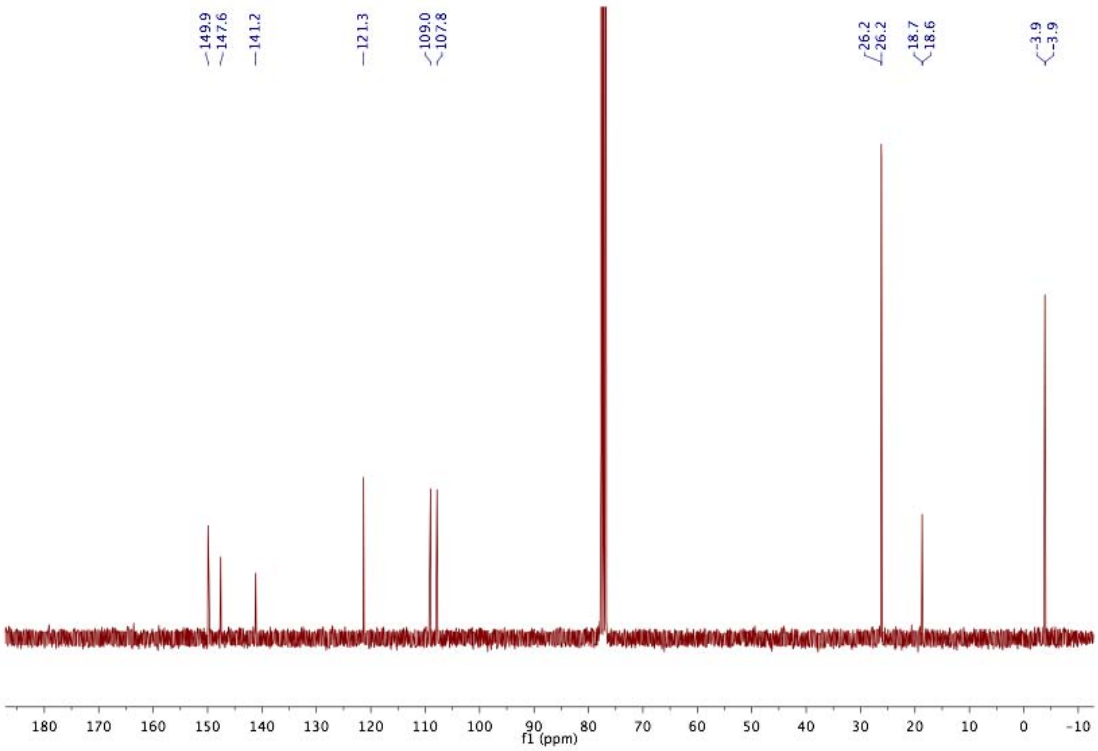

O
H
MeO
OMe
OTBS
9.69
9.68
9.67
6.72
6.69
6.63
6.61
3.79
3.75
3.60
3.59
1.02
0.15
0.15
0.94
0.96
1.00
2.91
2.90
1.94
9.27
6.04
f1 (ppm)
200.4
152.0
150.9
138.9
122.6
118.8
107.5
60.3
55.6
45.2
26.0
18.9
-4.4
f1 (ppm)

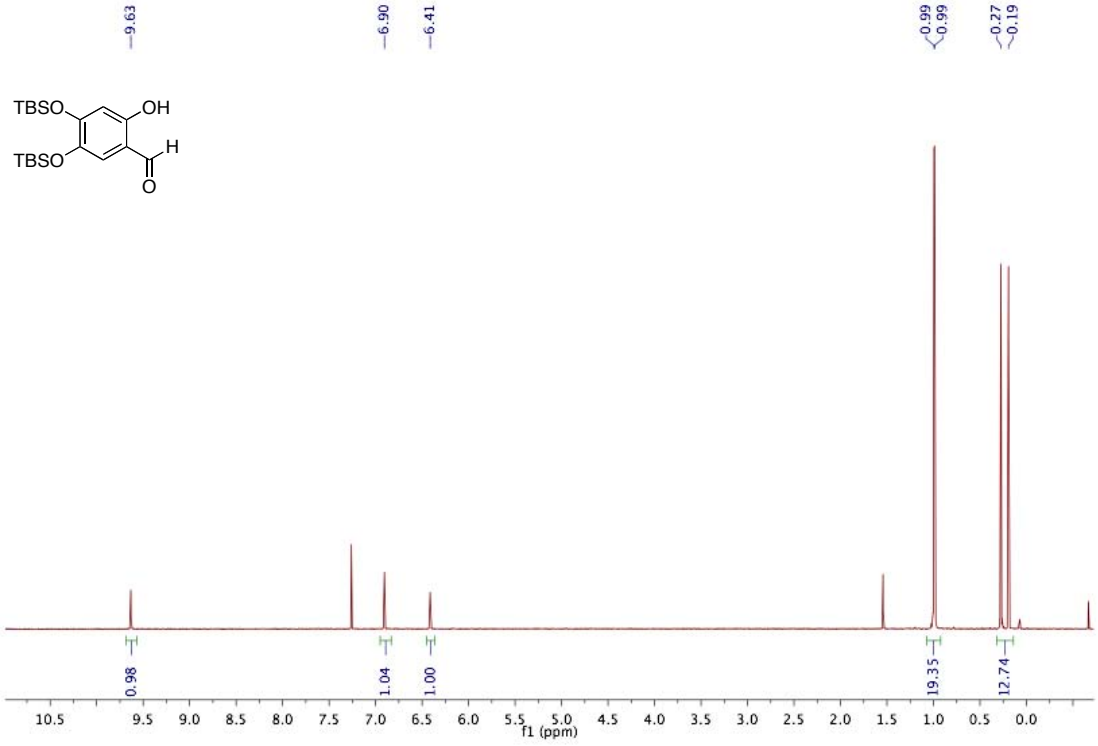

O
OH
MeO
OMe
OTBS
6.79
6.76
6.62
6.59
3.80
3.78
3.62
1.01
0.14
1.00
0.99
2.90
3.00
1.92
9.25
6.00
f1 (ppm)
151.91
150.40
138.68
122.37
120.11
107.34
60.47
55.56
35.77
26.02
18.84
4.40
f1 (ppm)

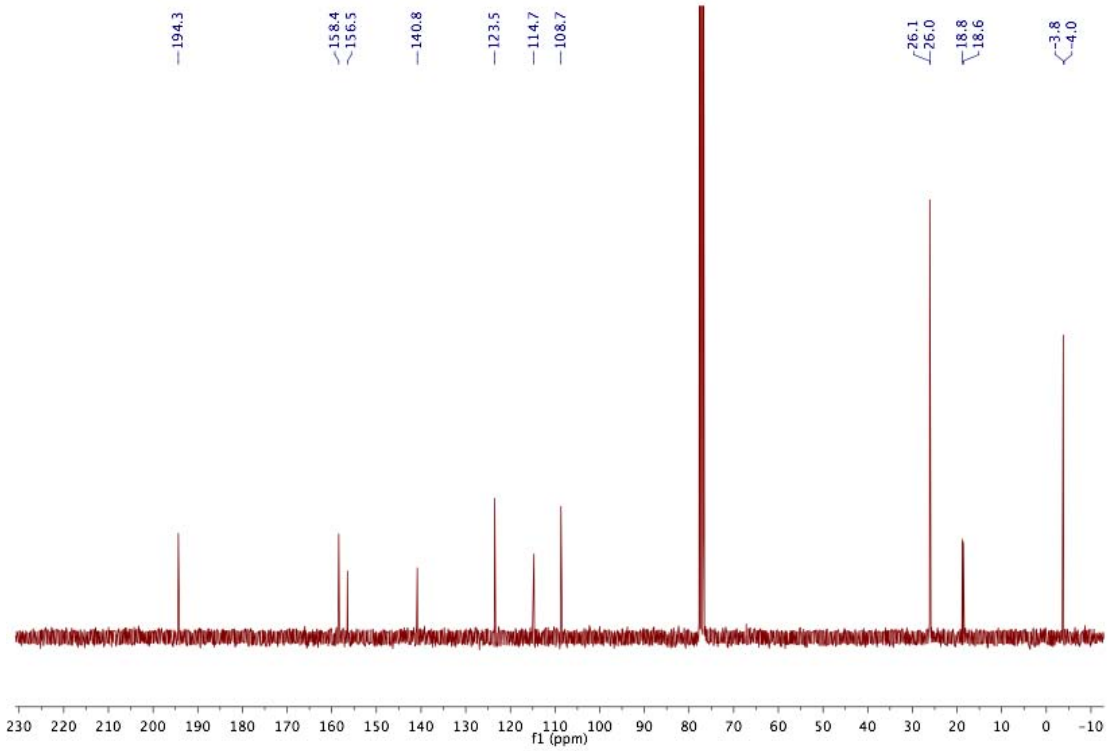

TBSO
TBSO
O
H
8.26
8.26
6.82
6.79
6.64
6.64
6.63
6.63
6.62
6.61
6.59
6.58
0.98
0.98
0.21
0.20
0.98
1.00
0.98
1.08
17.75
12.26
f1 (ppm)

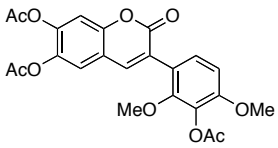

159.8
147.6
145.6
143.8
121.1
114.4
113.6
26.1
26.1
18.6
-3.9
-3.9
f1 (ppm)


TBSO
OH
TBSO
6.68
6.65
6.38
6.37
6.30
6.29
6.27
6.26
4.32
0.98
0.97
0.20
0.16
1.02
1.00
1.04
1.04
19.58
12.86
f1 (ppm)

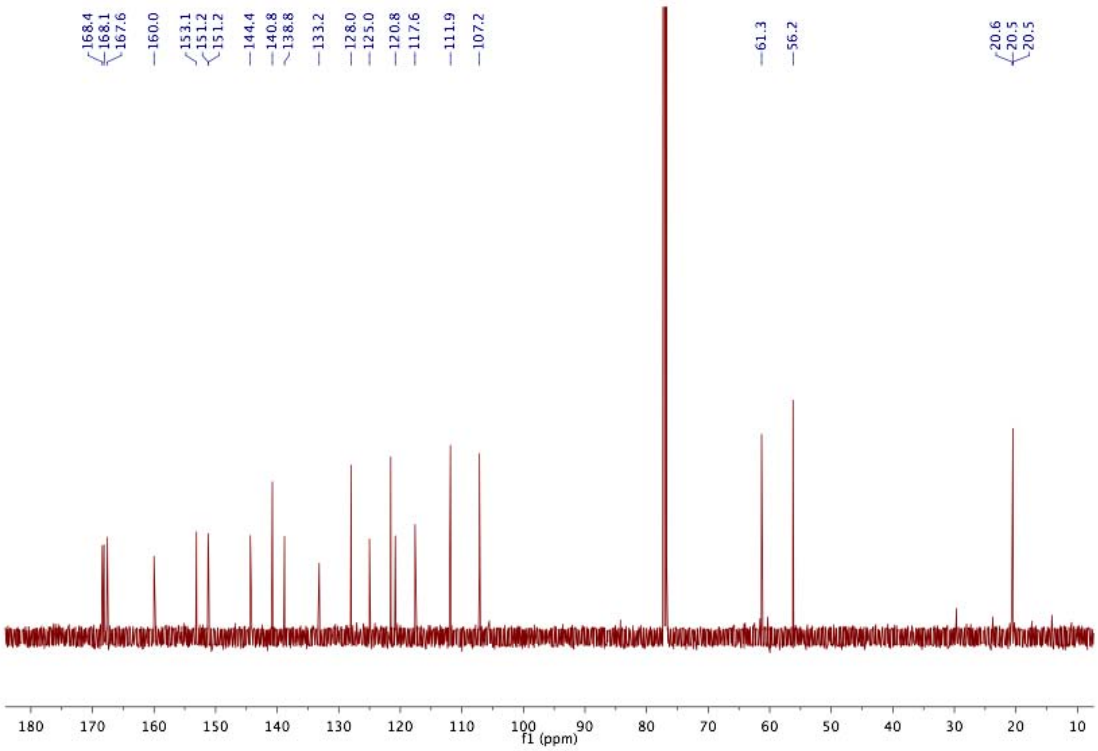

149.9
147.6
141.2
121.3
109.0
107.8
26.2
26.2
18.7
18.6
-3.9
-3.9
f1 (ppm)

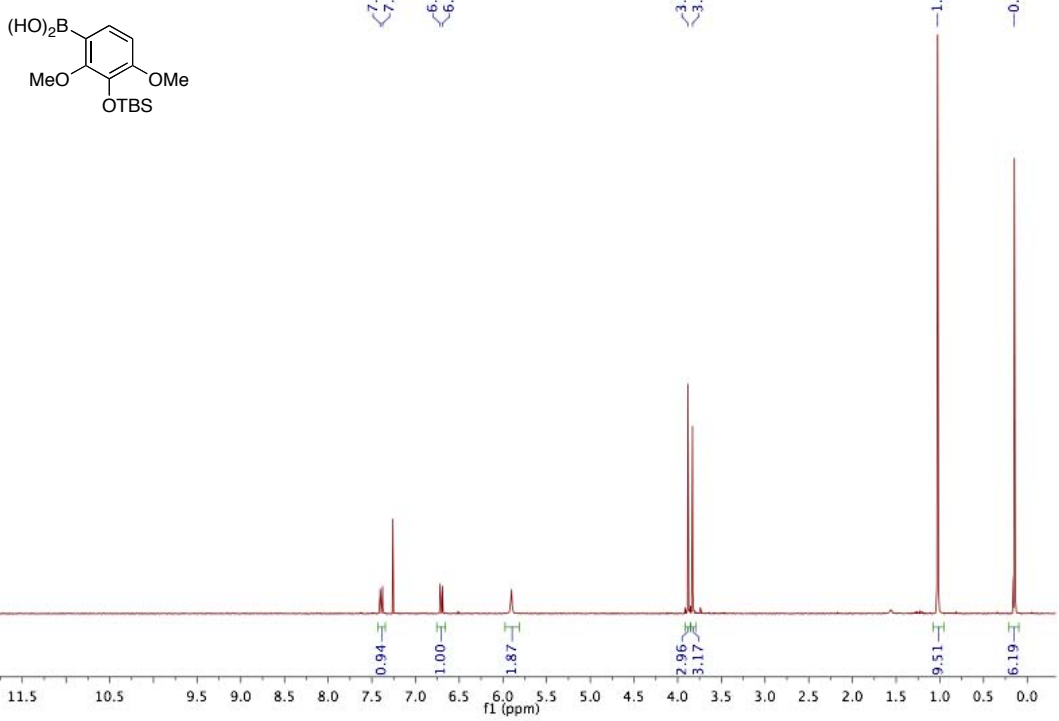

9.63
6.90
6.41
0.99
0.99
0.27
0.19
TBSO
OH
TBSO
H
O
0.98
1.04
1.00
19.35
12.74
f1 (ppm)

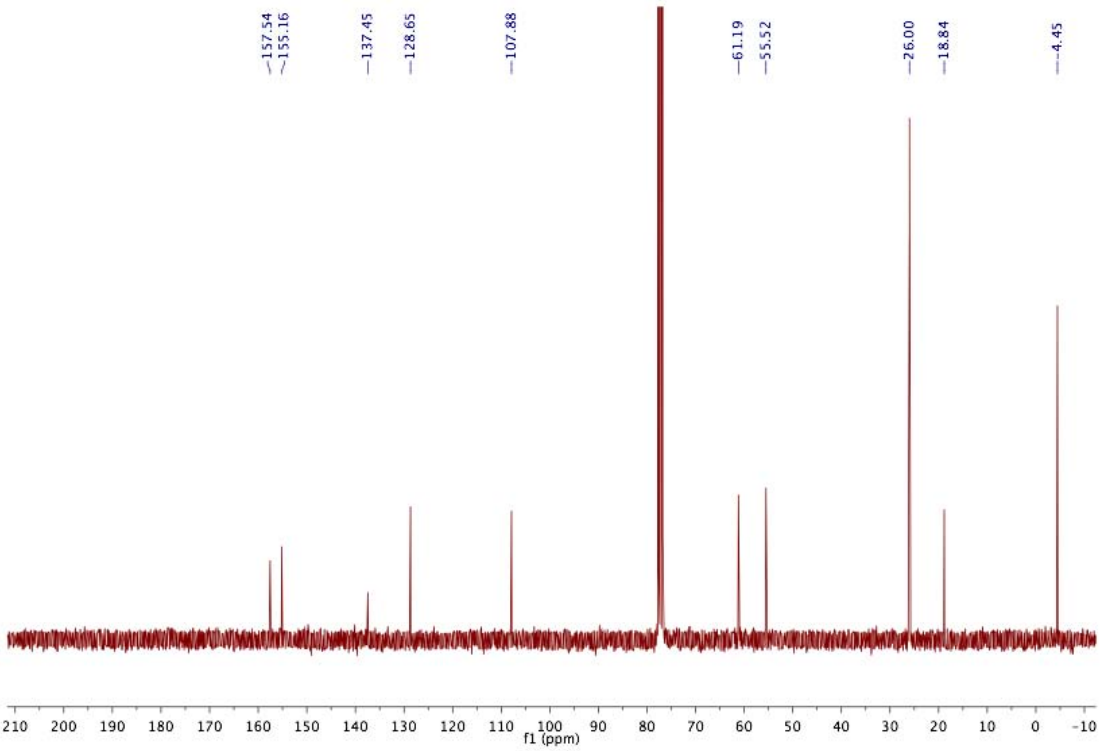

194.3
158.4
156.5
140.8
123.5
114.7
108.7
26.1
26.0
18.8
18.6
-3.8
-4.0
f1 (ppm)

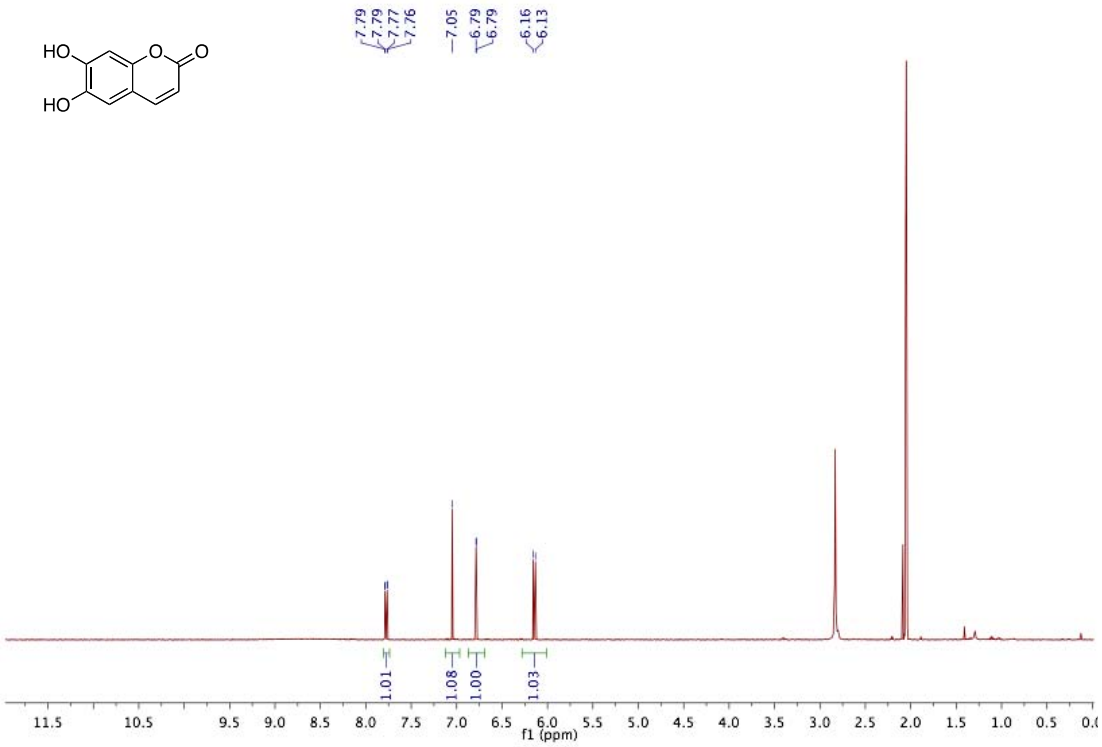

AcO
AcO
O
O
MeO
OMe
OAc

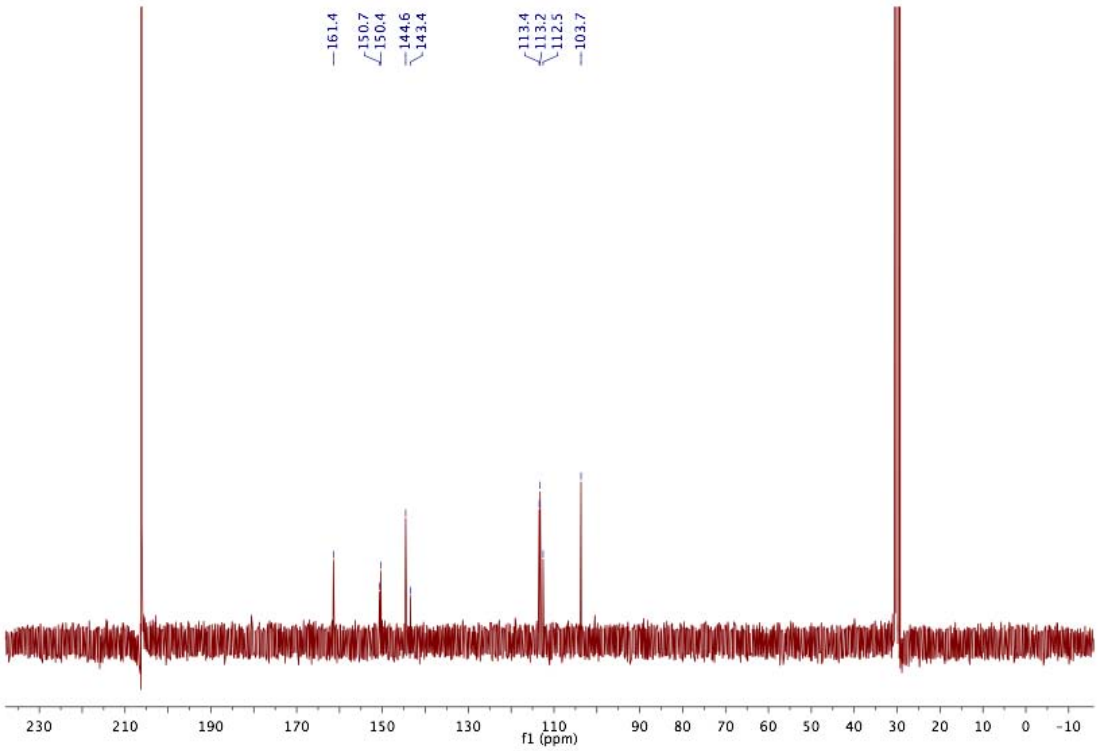
7.76
7.33
7.31
7.30
7.24
6.80
6.79
3.86
3.73
2.37
2.34
2.32
0.96
0.95
1.00
0.95
1.00
3.02
2.93
3.06
2.92
3.03
f1 (ppm)

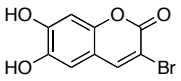

168.4
168.1
167.6
160.0
153.1
151.2
151.2
144.4
140.8
138.8
133.2
128.0
125.0
120.8
117.6
111.9
107.2
61.3
56.2
20.6
20.5
20.5
f1 (ppm)


(HO)2B
MeO
OMe
OTBS
7.41
7.38
6.72
6.69
3.88
3.83
1.03
0.15
0.94
1.00
1.87
2.96
3.17
9.51
6.19
f1 (ppm)

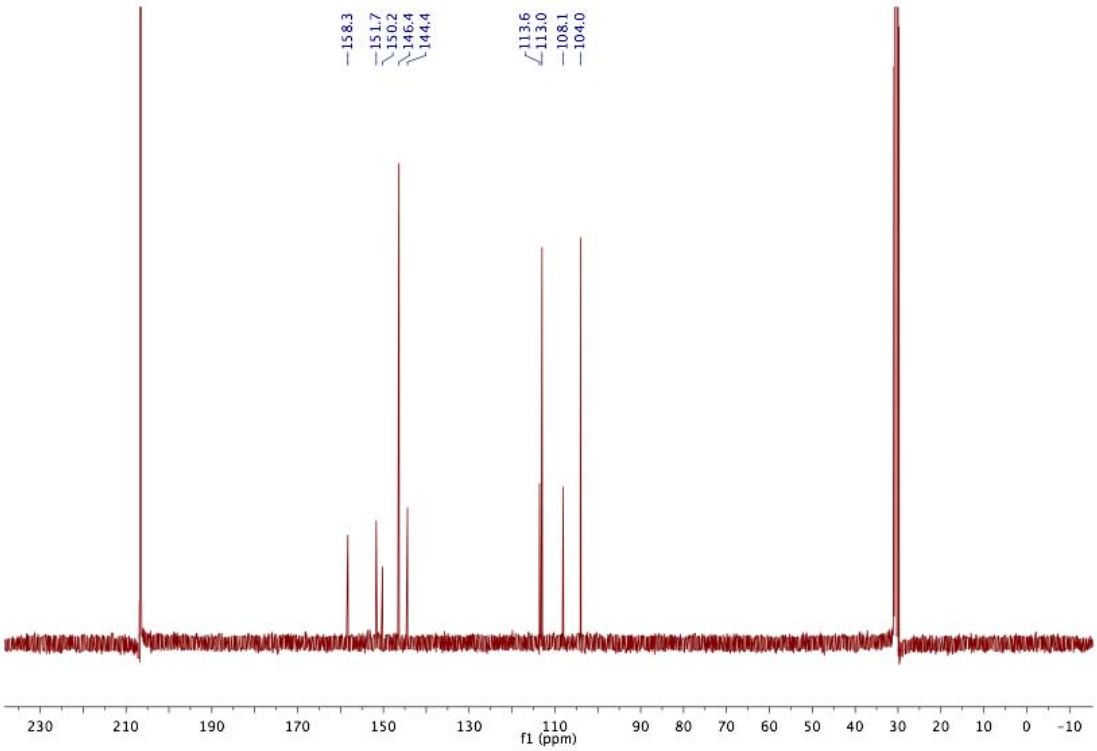

157.54
155.16
137.45
128.65
107.88
61.19
55.52
26.00
18.84
4.45
f1 (ppm)

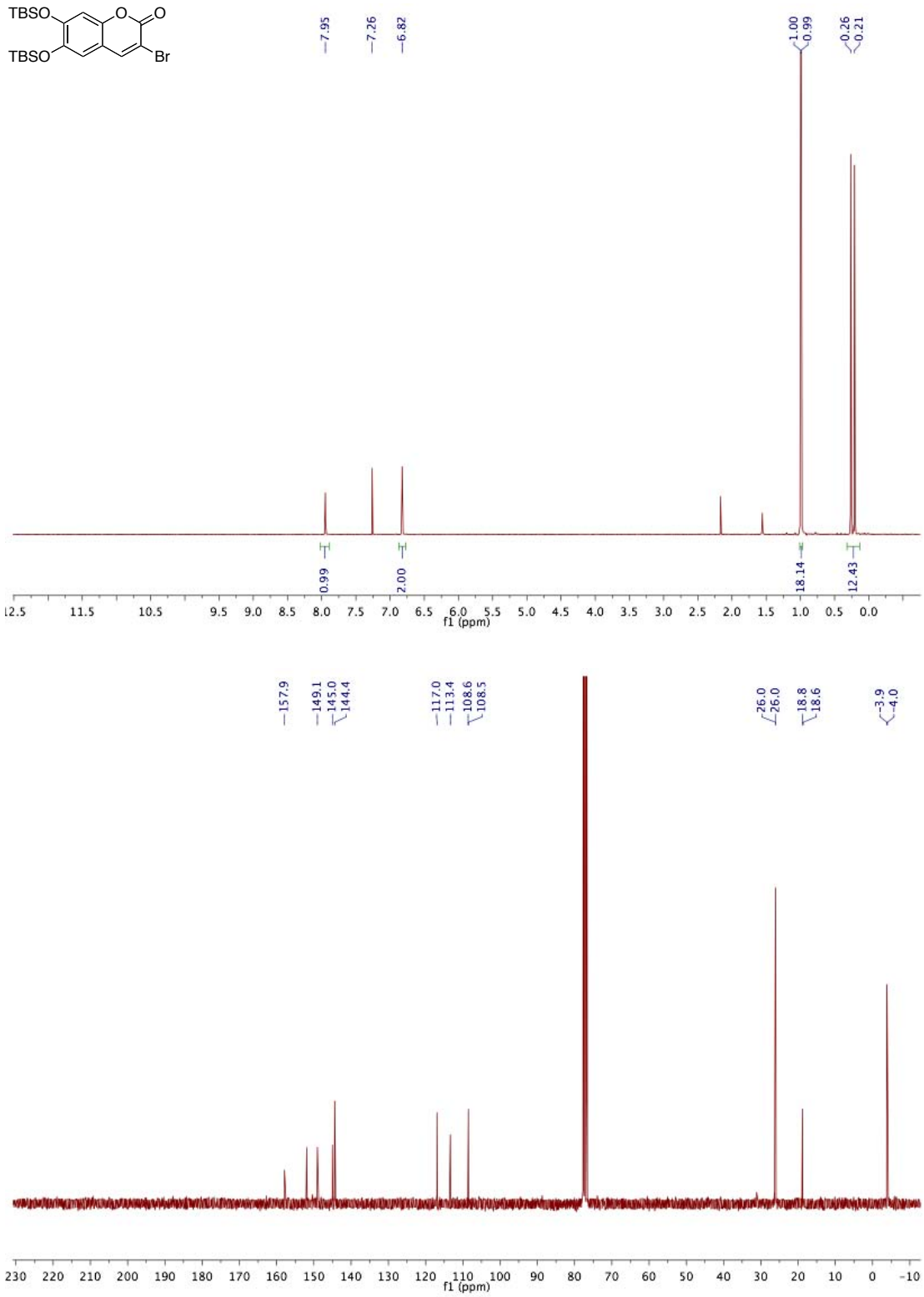

HO
HO
O
O
7.79
7.79
7.77
7.76
7.05
6.79
6.79
6.16
6.13
1.01
1.08
1.00
1.03
f1 (ppm)

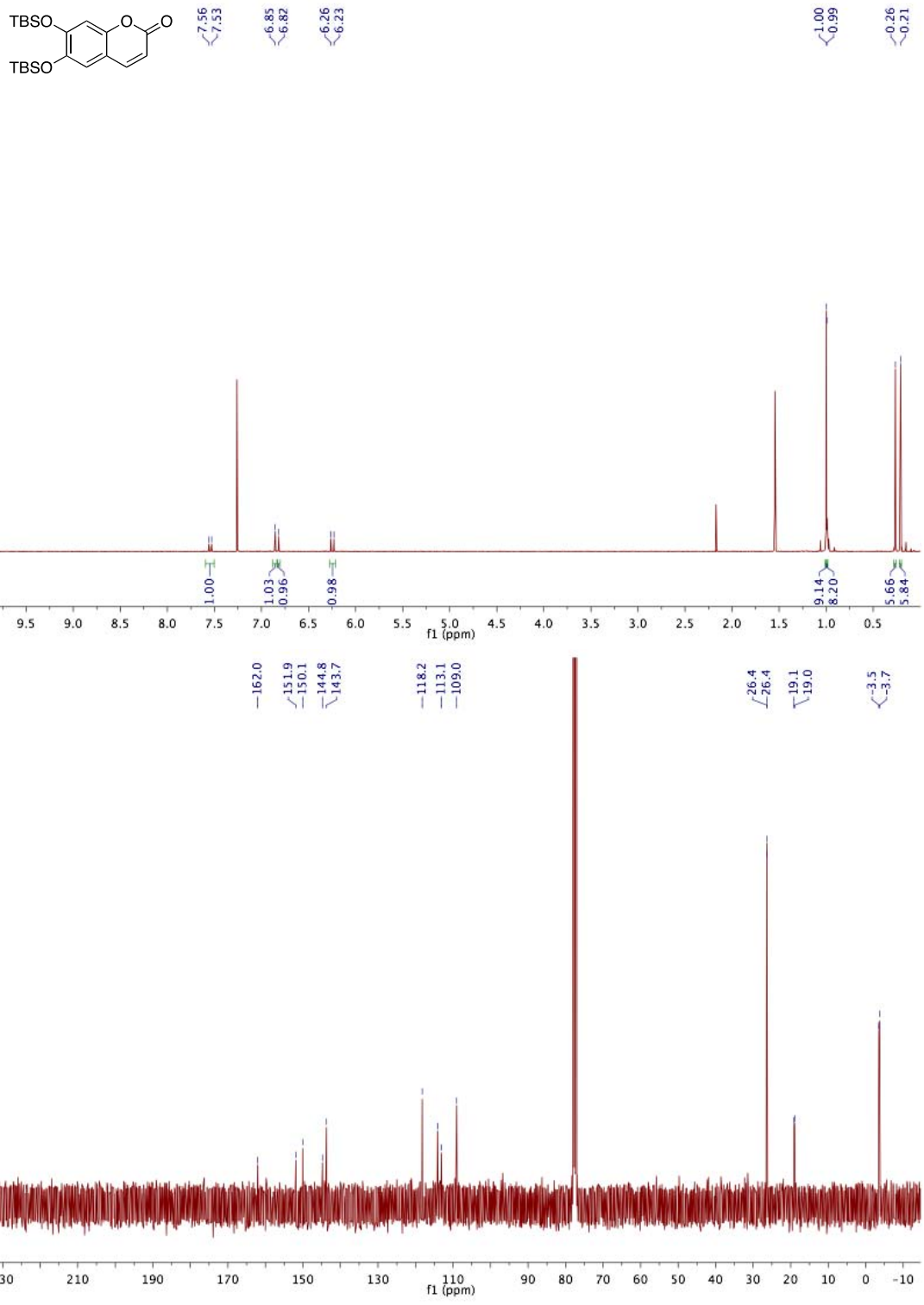

161.4
150.7
150.4
144.6
143.4
113.4
113.2
112.5
103.7
f1 (ppm)

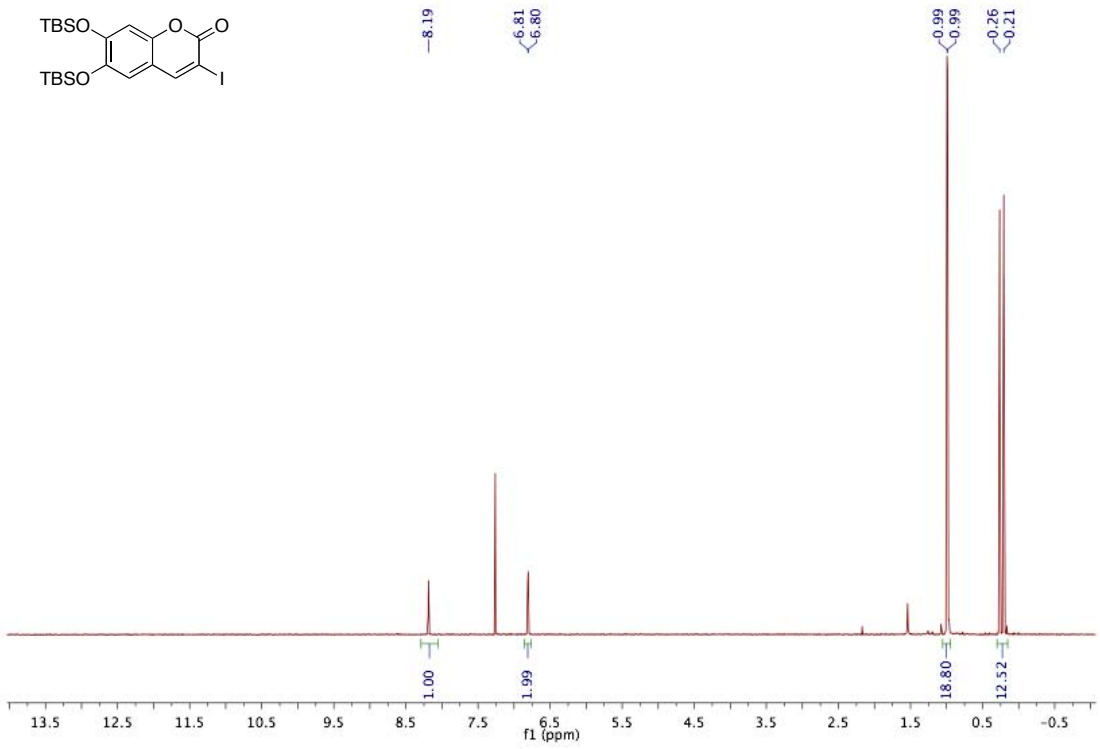

HO
HO
O
O
Br

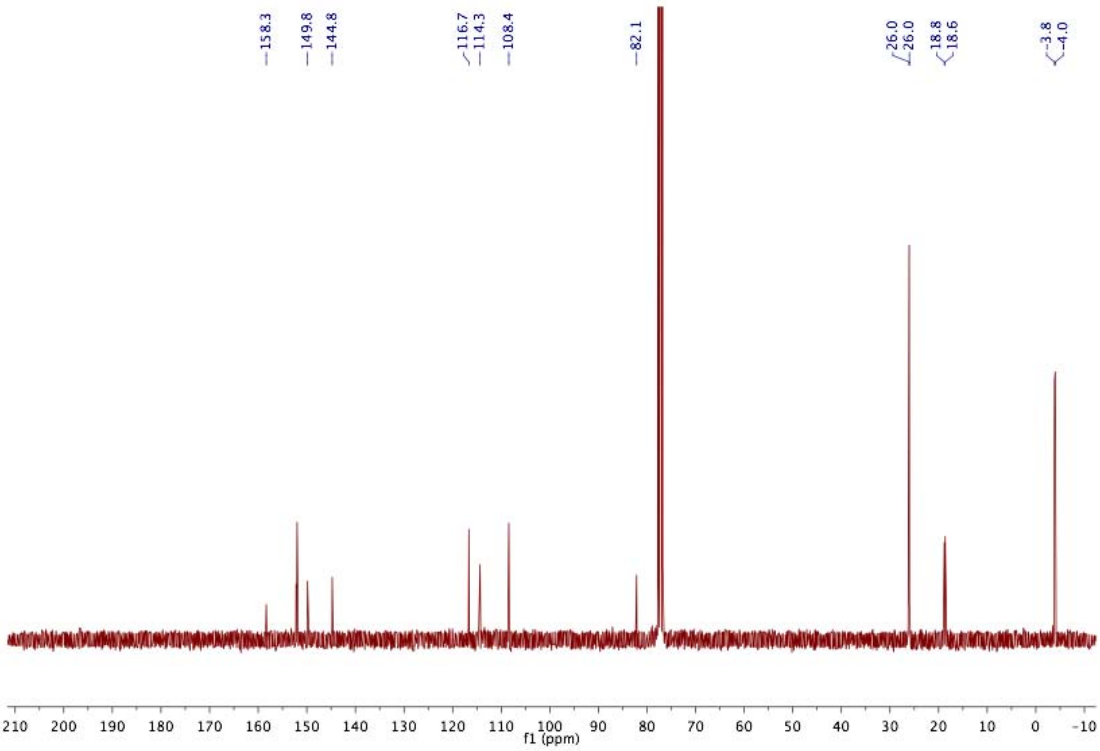
8.86
8.25
7.07
6.83
1.65
1.00
1.09
1.02
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

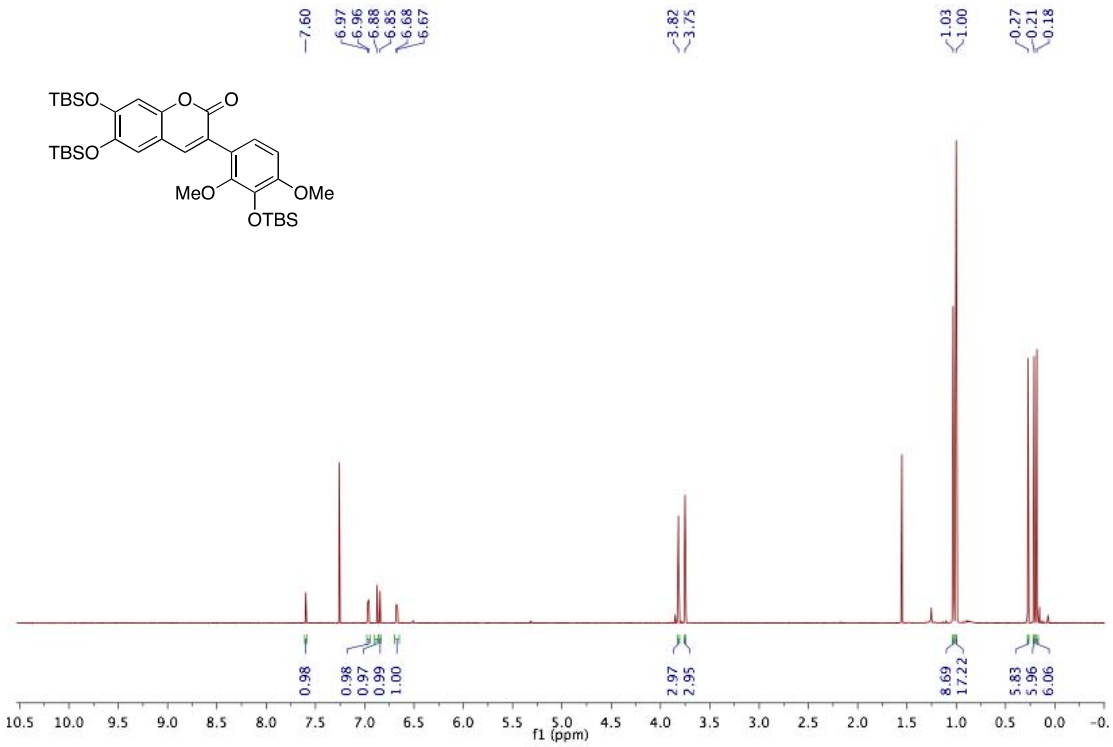

158.3
151.7
150.2
146.4
144.4
113.6
113.0
108.1
104.0
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

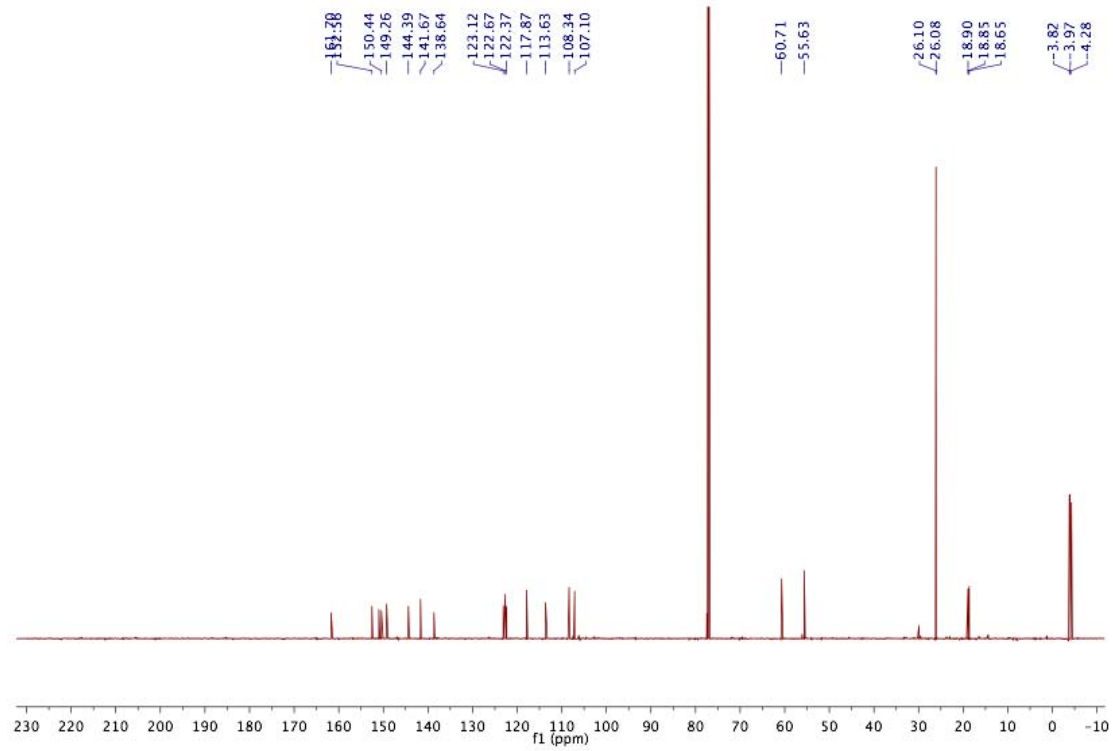

TBSO
TBSO
O
O
Br
7.95
7.26
6.82
1.00
0.99
0.26
0.21
0.99
2.00
18.14
12.43
f1 (ppm)
157.9
149.1
145.0
144.4
117.0
113.4
108.6
108.5
26.0
26.0
18.8
18.6
-3.9
-4.0
f1 (ppm)

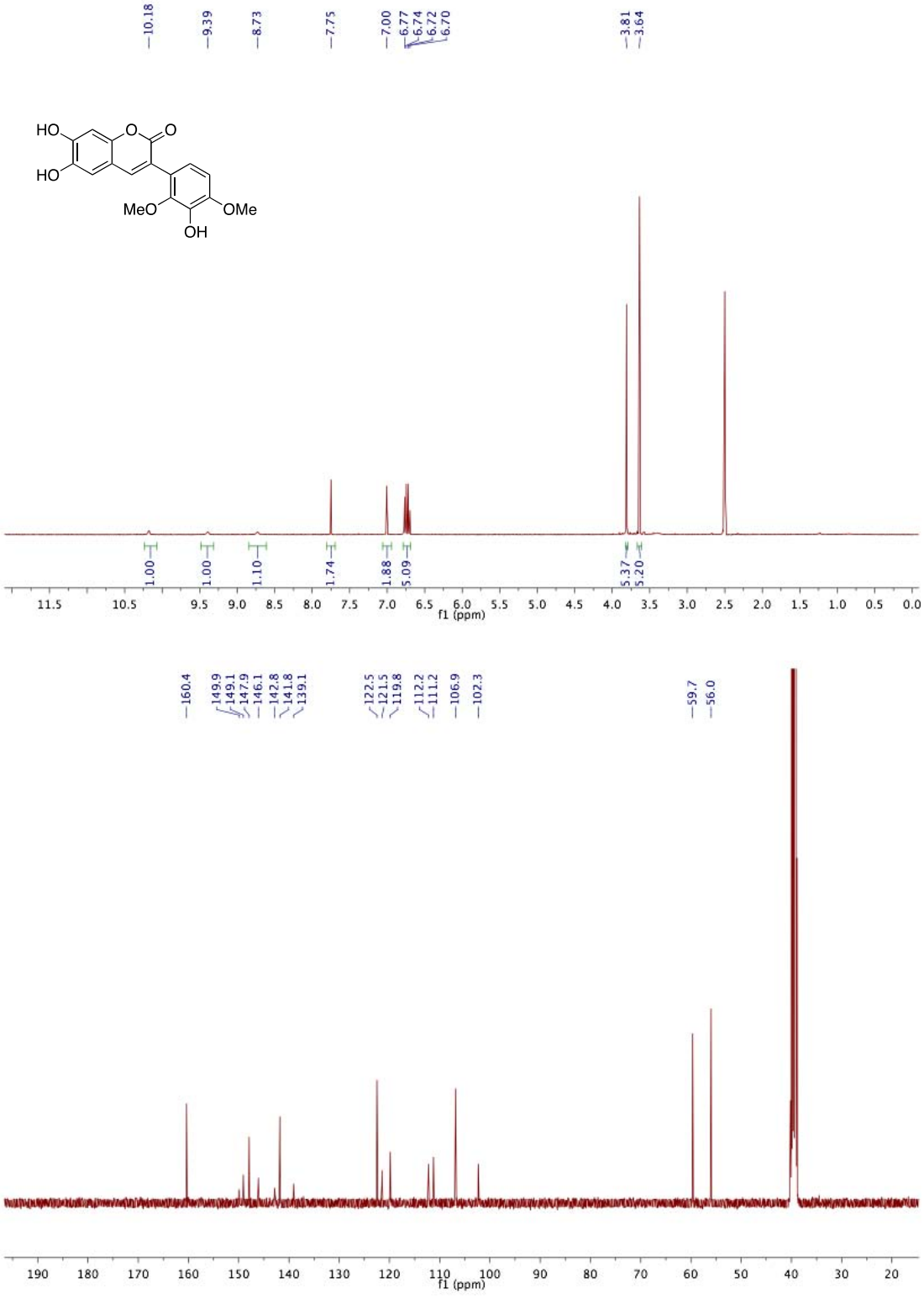

TBSO
TBSO
O
O
7.56
7.53
6.85
6.82
6.26
6.23
1.00
0.99
0.26
0.21
1.00
1.03
0.96
0.98
9.14
8.20
5.66
5.84
f1 (ppm)
162.0
151.9
150.1
144.8
143.7
118.2
113.1
109.0
26.4
26.4
19.1
19.0
-3.5
-3.7
f1 (ppm)

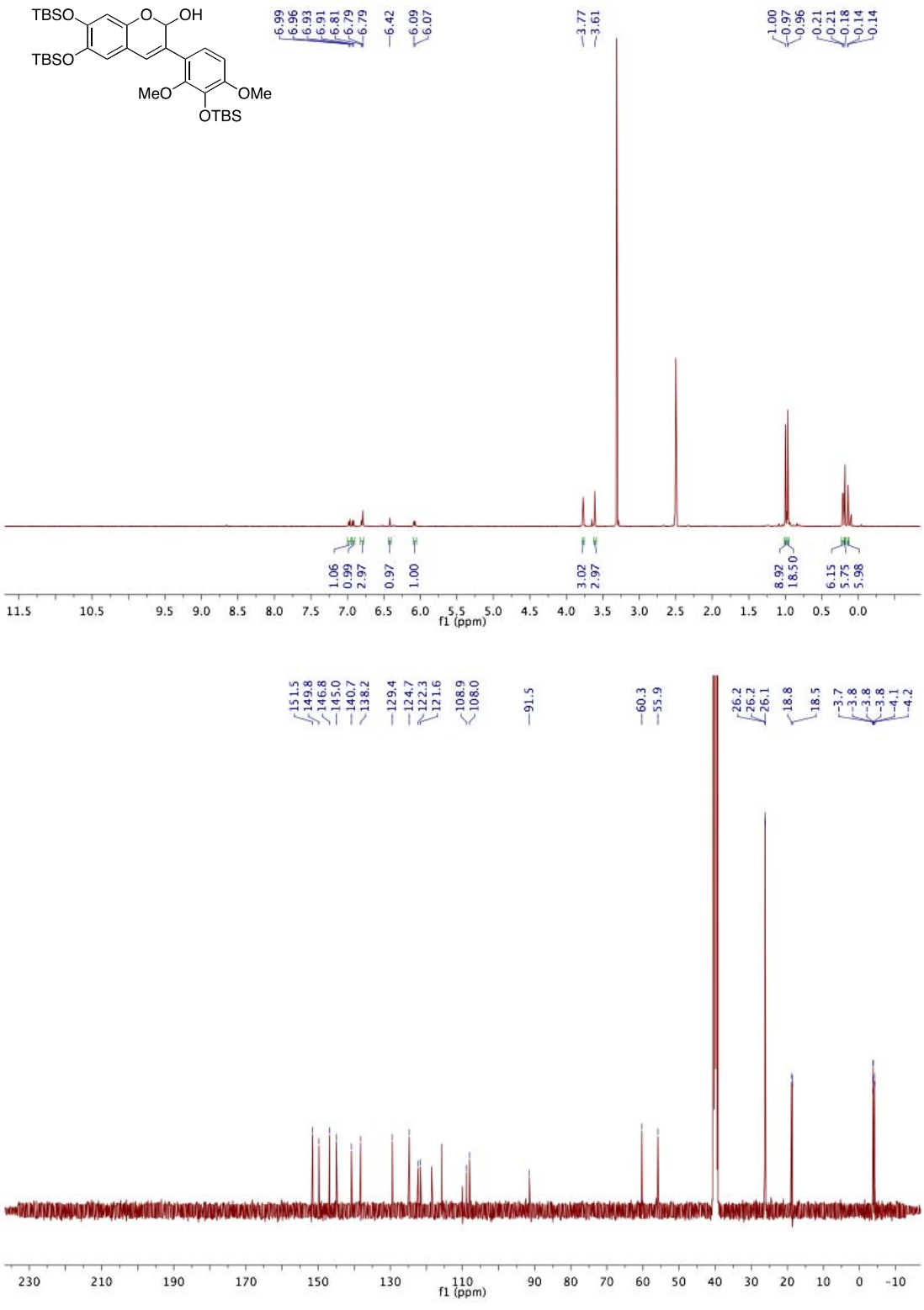

TBSO
TBSO
O
O
I
8.19
6.81
6.80
0.99
0.99
0.26
0.21
1.00
1.99
18.80
12.52
f1 (ppm)

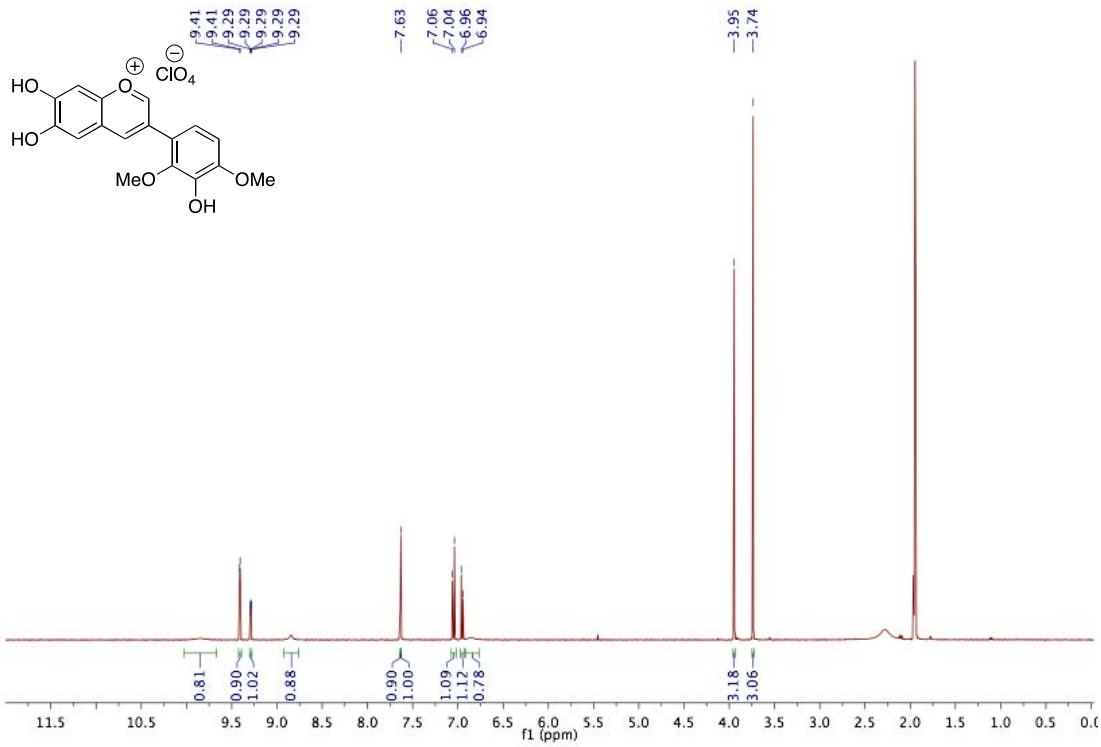

158.3
149.8
144.8
116.7
114.3
108.4
82.1
26.0
26.0
18.8
18.6
-3.8
-4.0
f1 (ppm)

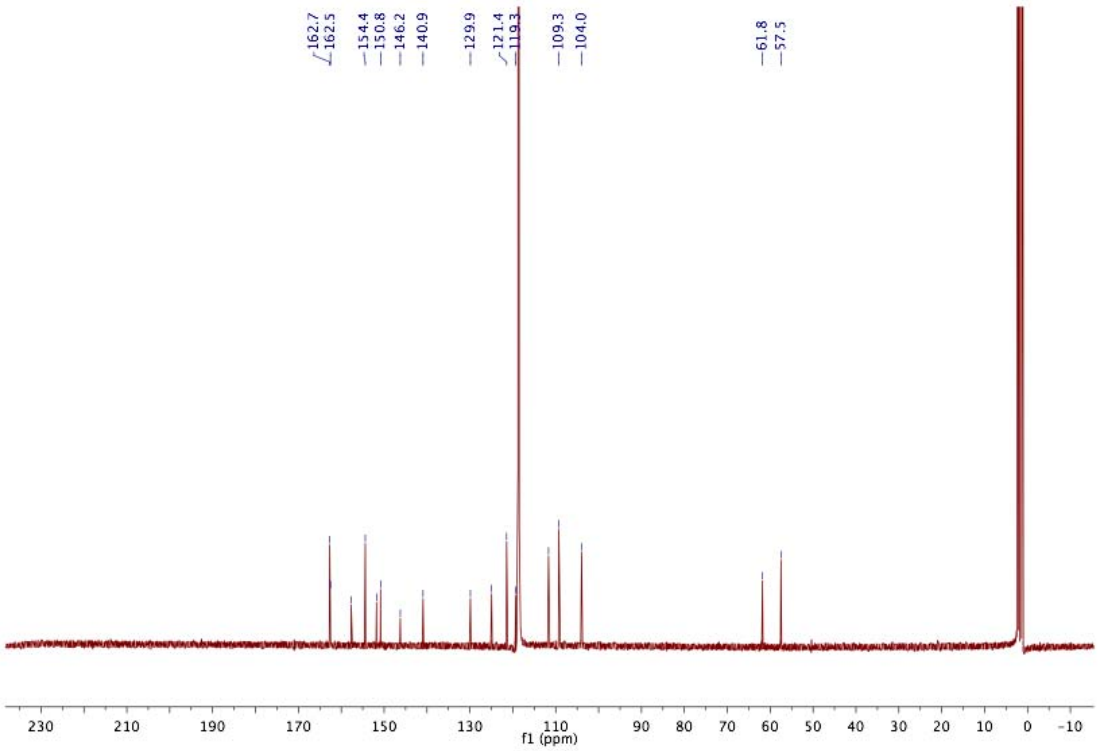

TBSO
TBSO
O
O
MeO
OMe
OTBS
f1 (ppm)

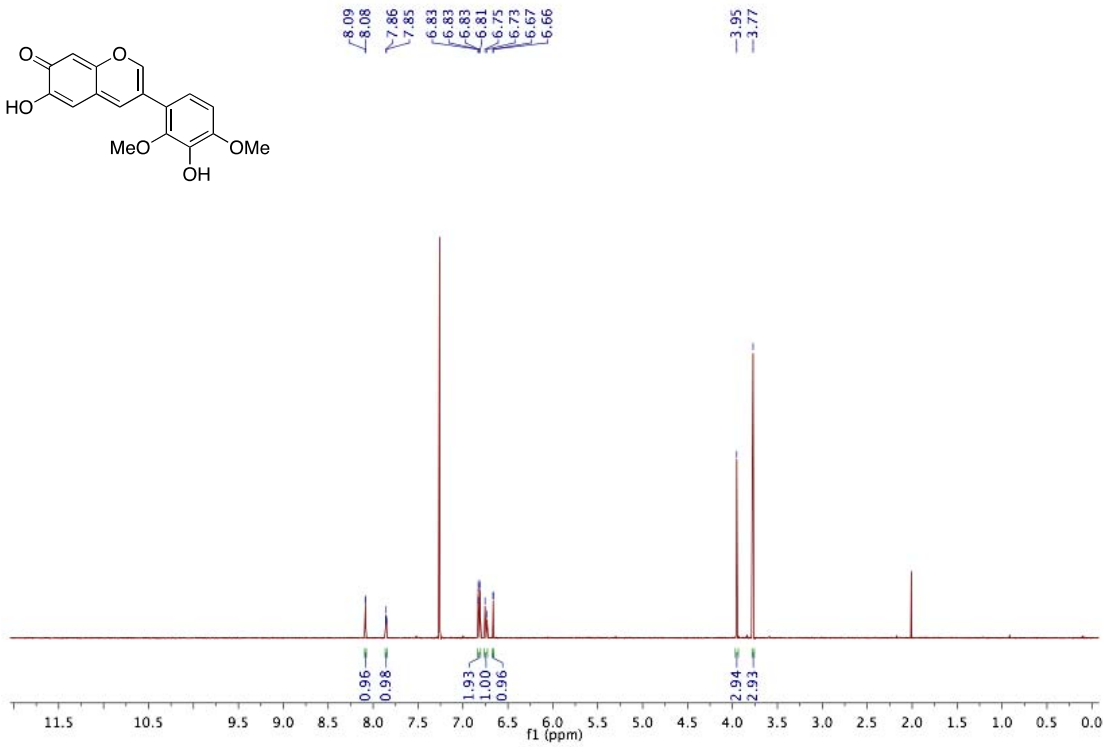

f1 (ppm)

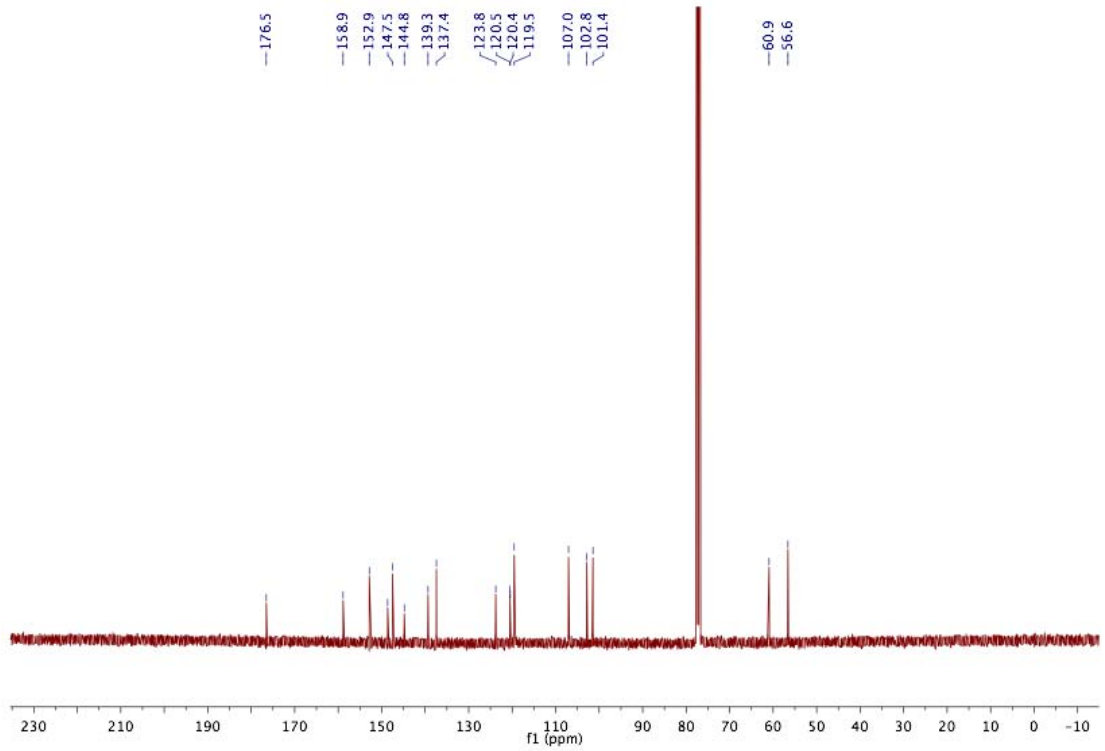

10.18
9.39
8.73
7.75
7.00
6.77
6.74
6.72
6.70
3.81
3.64
HO
HO
O
O
MeO
OMe
OH
1.00
1.00
1.10
1.74
1.88
5.09
5.37
5.20
f1 (ppm)
160.4
149.9
149.1
147.9
146.1
142.8
141.8
139.1
122.5
121.5
119.8
112.2
111.2
106.9
102.3
59.7
56.0
f1 (ppm)

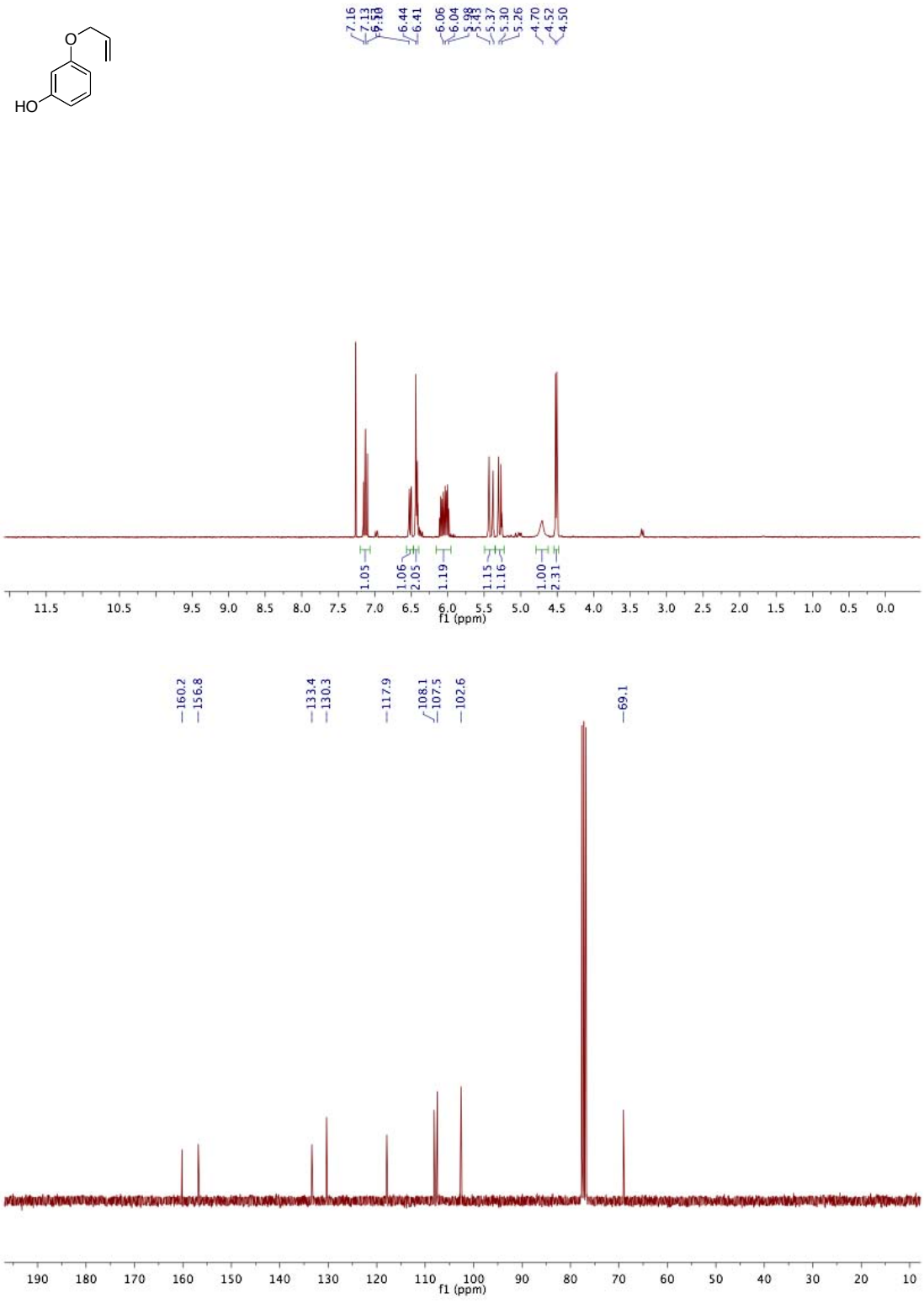

TBSO
TBSO
O
OH
MeO
OMe
OTBS
6.99
6.96
6.93
6.91
6.81
6.79
6.79
6.42
6.09
6.07
3.77
3.61
1.00
0.97
0.96
0.21
0.21
0.18
0.14
0.14
1.06
0.99
2.97
0.97
1.00
3.02
2.97
8.92
18.50
6.15
5.75
5.98
f1 (ppm)
151.5
149.8
146.8
145.0
140.7
138.2
129.4
124.7
122.3
121.6
108.9
108.0
91.5
60.3
55.9
26.2
26.2
26.1
18.8
18.5
-3.7
-3.8
-3.8
-3.8
-4.1
-4.2
f1 (ppm)

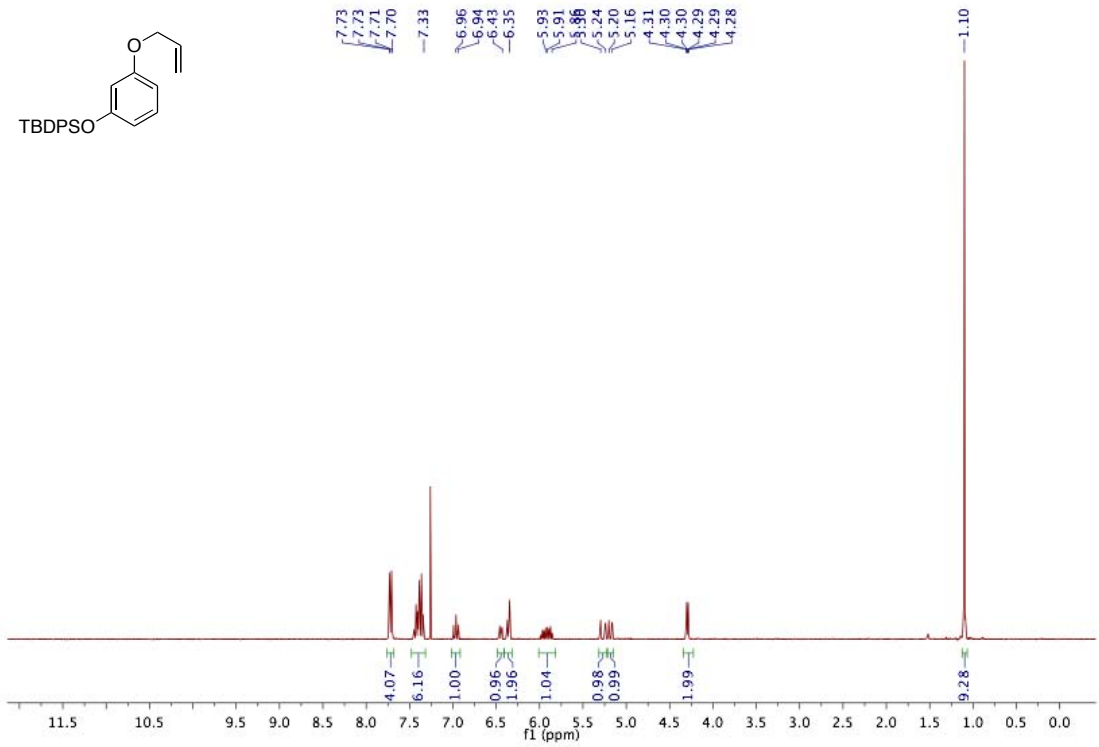

HO
HO
O
ClO4
MeO
OMe
OH
9.41
9.41
9.29
9.29
9.29
9.29
9.29
7.63
7.06
7.04
6.96
6.94
3.95
3.74
0.81
0.90
1.02
0.88
0.90
1.00
1.09
1.12
0.78
3.18
3.06
f1 (ppm)

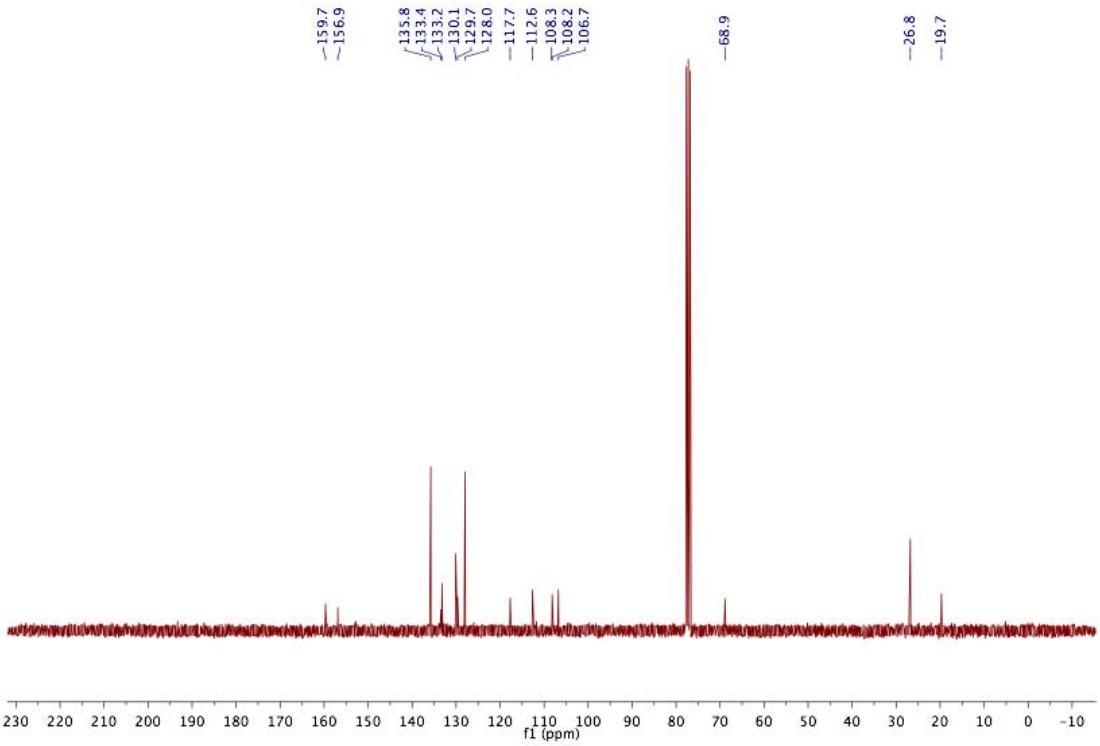

162.7
162.5
154.4
150.8
146.2
140.9
129.9
121.4
119.3
109.3
104.0
61.8
57.5
f1 (ppm)

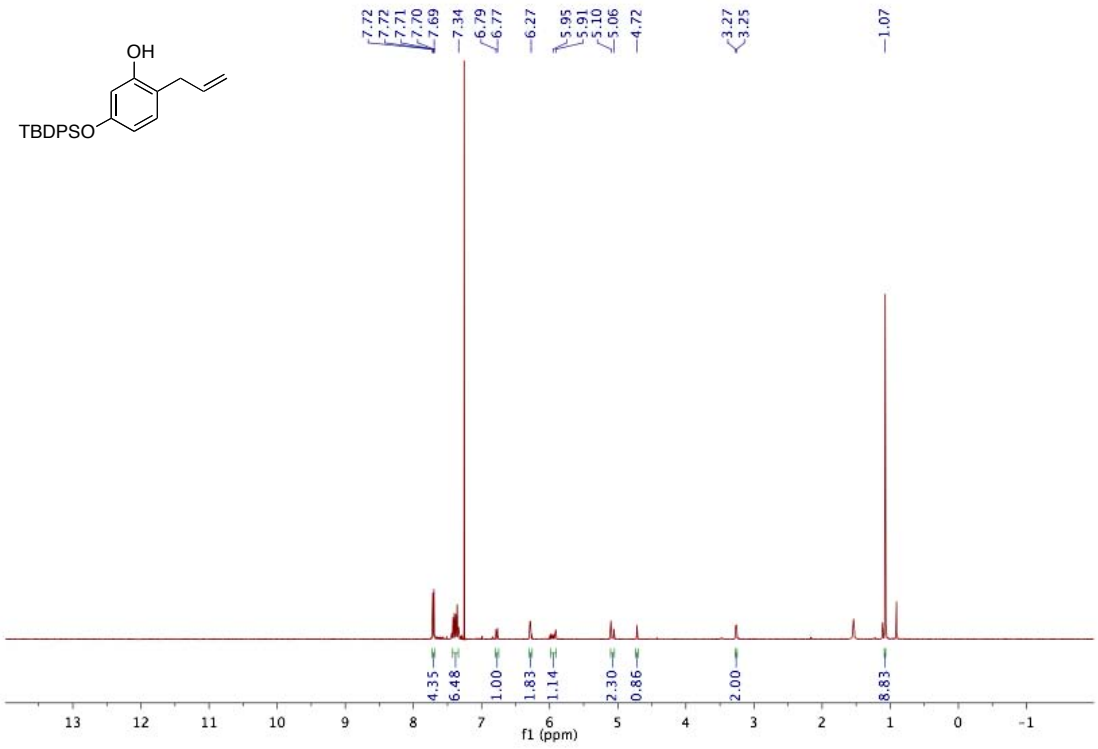

O
O
HO
MeO
OMe
OH
8.09
8.08
7.86
7.85
6.83
6.83
6.83
6.81
6.75
6.73
6.67
6.66
3.95
3.77
0.96
0.98
1.93
1.00
0.96
2.94
2.93
f1 (ppm)

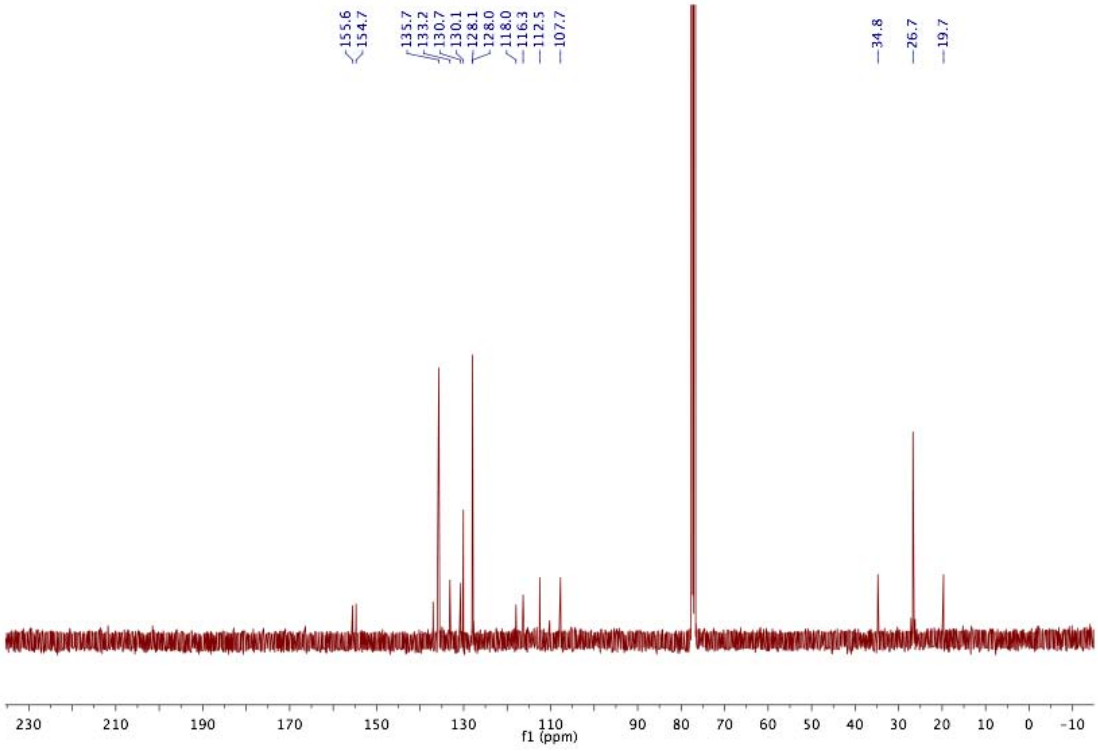

176.5
158.9
152.9
147.5
144.8
139.3
137.4
123.8
120.5
120.4
119.5
107.0
102.8
101.4
60.9
56.6
f1 (ppm)

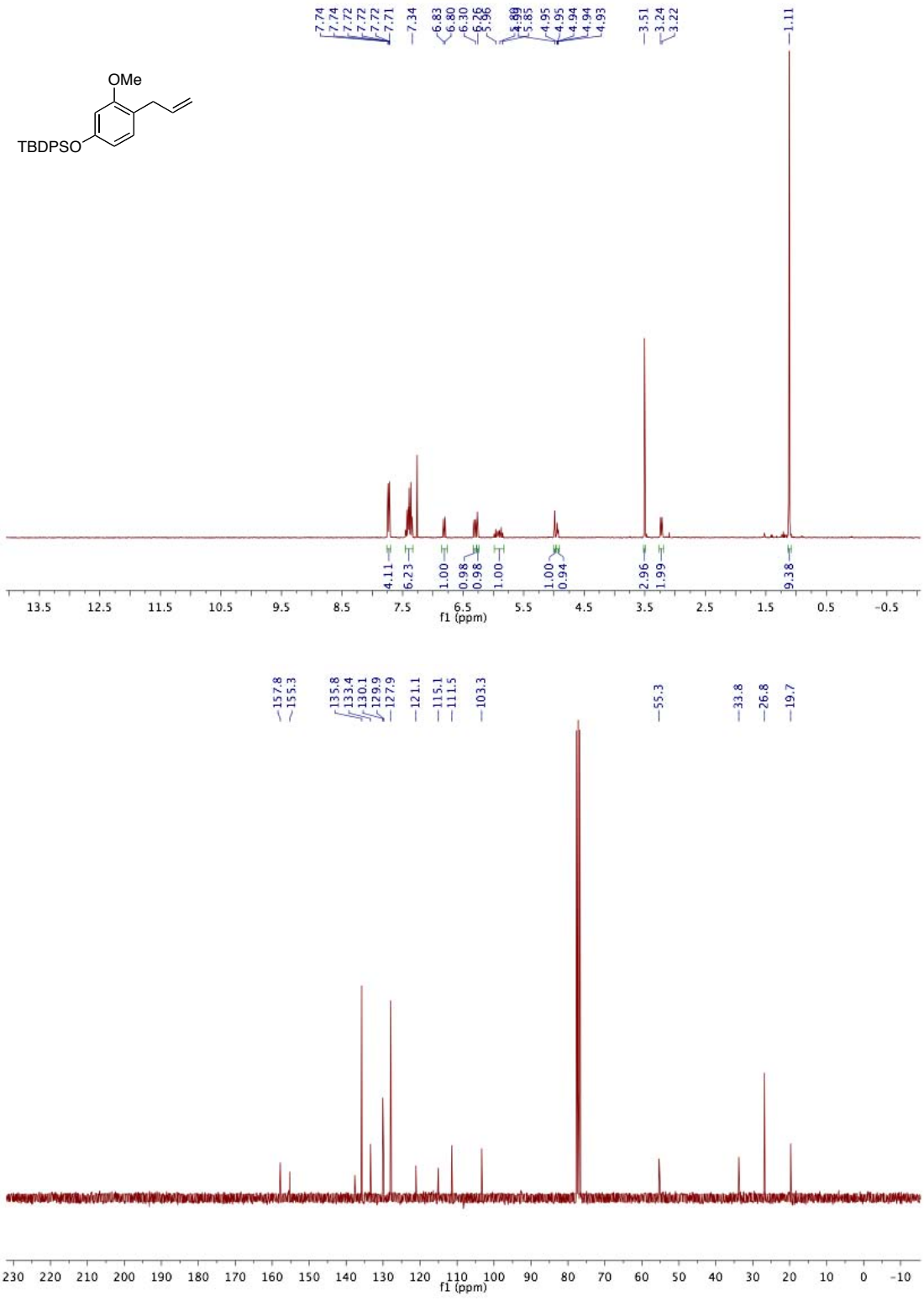

HO
O
7.16
7.13
6.44
6.41
6.06
6.04
5.37
5.30
5.26
4.70
4.52
4.50
1.05
1.06
2.05
1.19
1.15
1.16
1.00
2.31
f1 (ppm)
160.2
156.8
133.4
130.3
117.9
108.1
107.5
102.6
69.1
f1 (ppm)

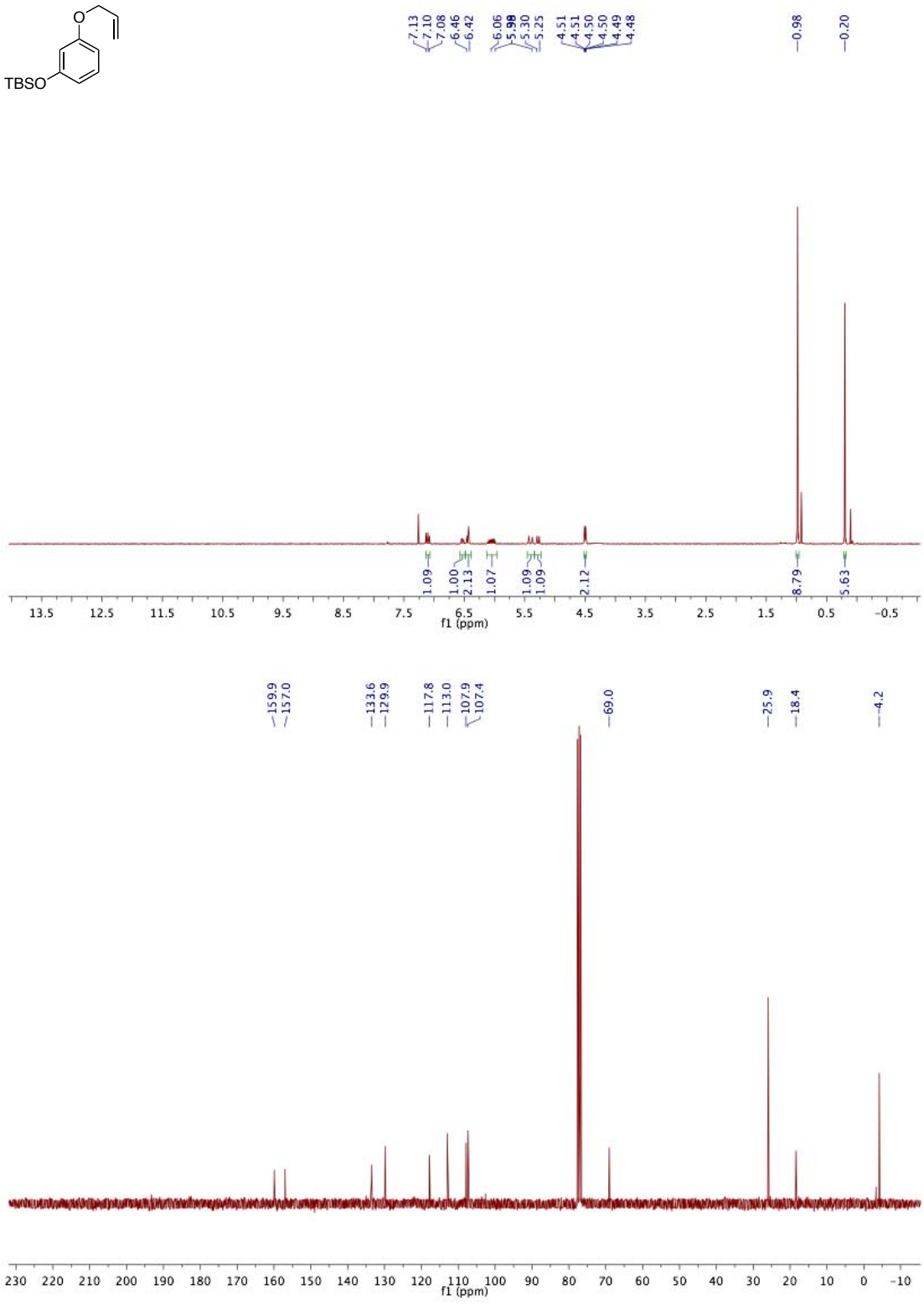

TBDPSO
O
7.73
7.73
7.71
7.70
7.33
6.96
6.94
6.43
6.35
5.93
5.91
5.24
5.20
5.16
4.31
4.30
4.29
4.29
4.28
1.10
4.07
6.16
1.00
0.96
1.96
1.04
0.98
0.99
1.99
9.28
f1 (ppm)

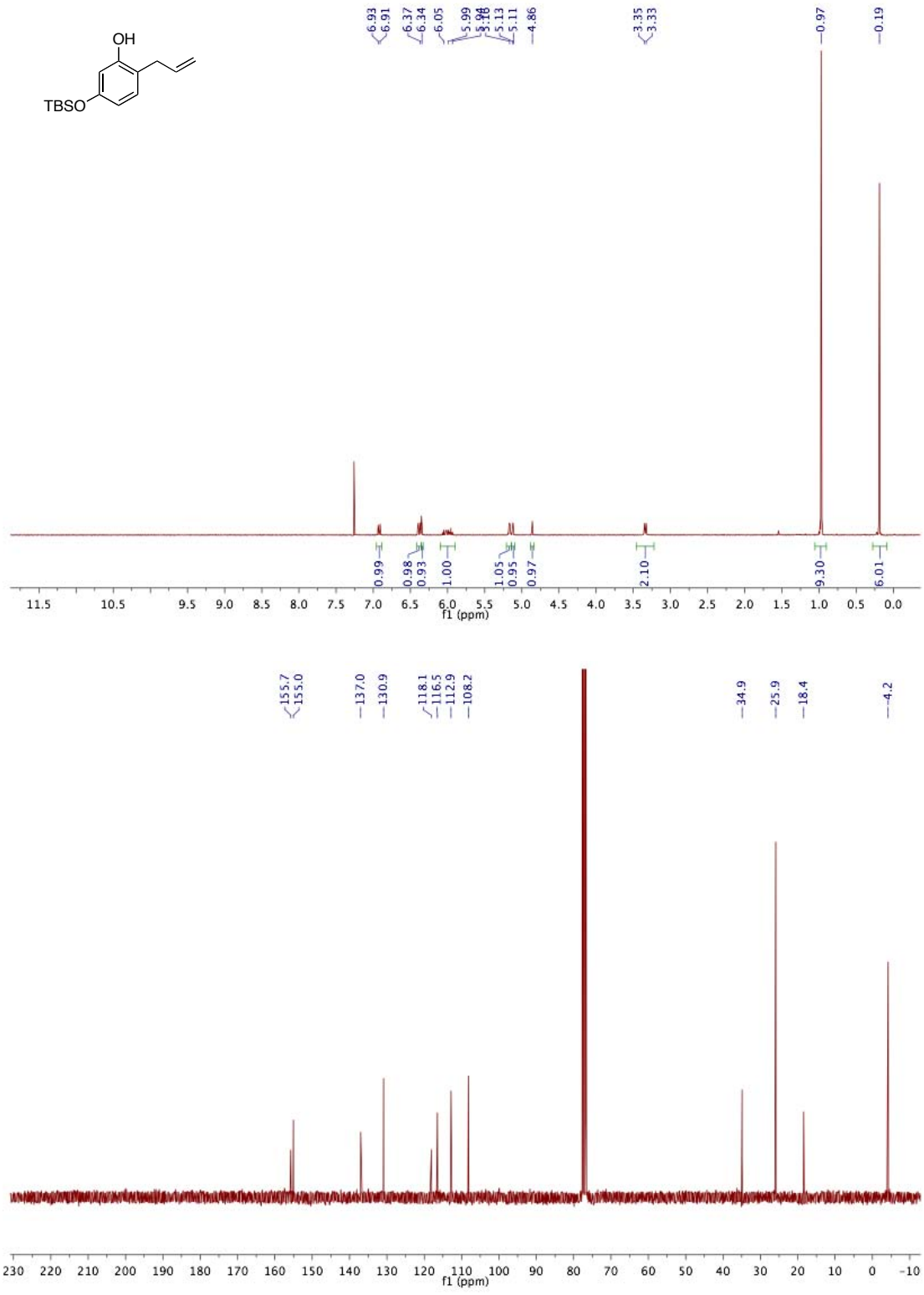

159.7
156.9
135.8
133.4
133.2
130.1
129.7
128.0
117.7
112.6
108.3
108.2
106.7
68.9
26.8
19.7
f1 (ppm)

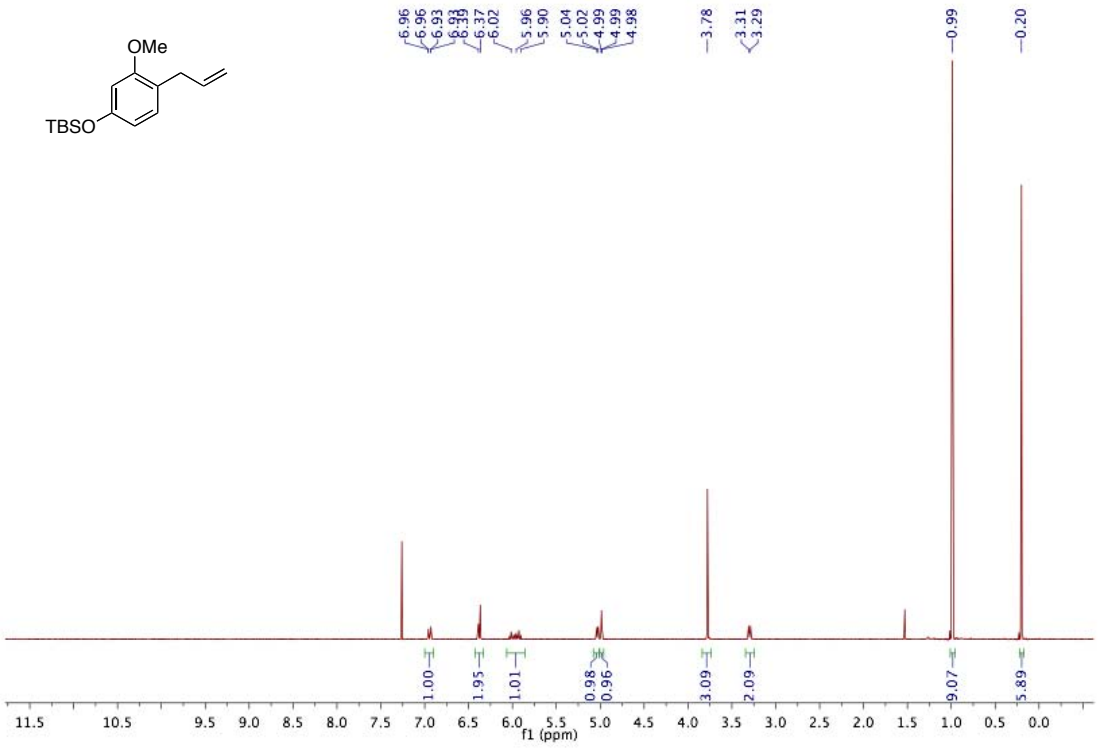

OH
TBDPSO
7.72
7.72
7.71
7.70
7.69
7.34
6.79
6.77
6.27
5.95
5.91
5.10
5.06
4.72
3.27
3.25
1.07
4.35
6.48
1.00
1.83
1.14
2.30
0.86
2.00
8.83
f1 (ppm)

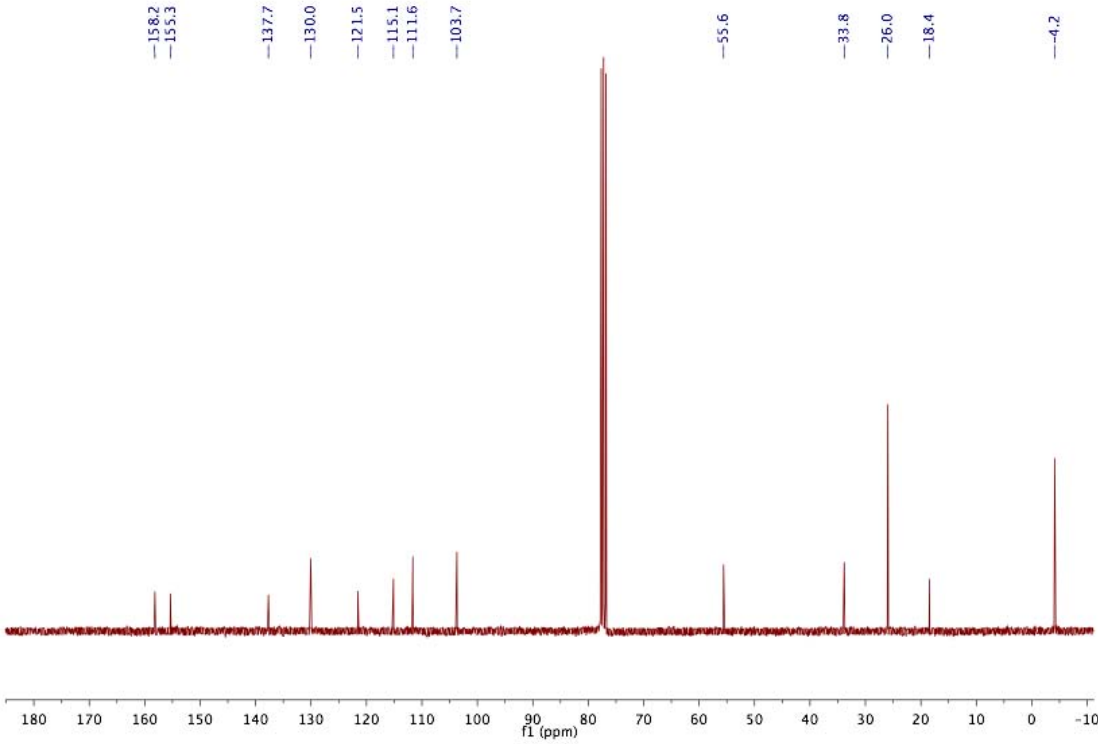

155.6
154.7
135.7
133.2
130.7
130.1
128.1
128.0
118.0
116.3
112.5
107.7
34.8
26.7
19.7
f1 (ppm)

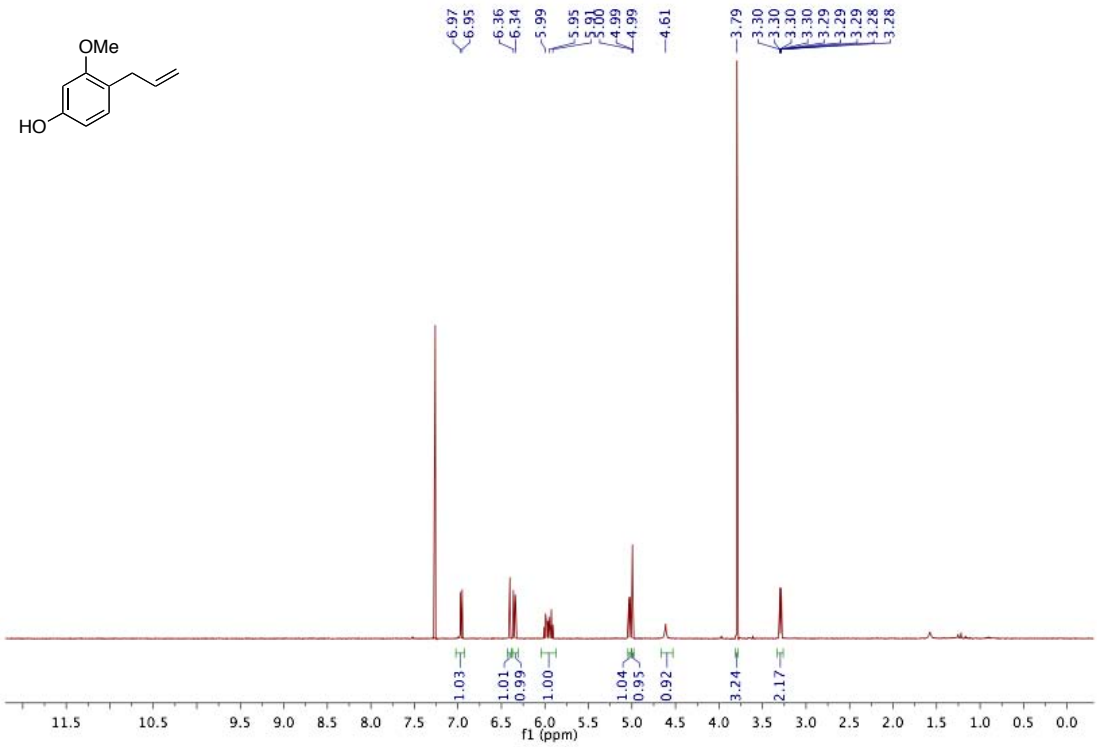

OMe
TBDPSO
7.74
7.74
7.72
7.72
7.72
7.71
7.34
6.83
6.80
6.30
5.96
4.95
4.95
4.94
4.94
4.93
3.51
3.24
3.22
1.11
4.11
6.23
1.00
0.98
0.98
1.00
1.00
0.94
2.96
1.99
9.38
f1 (ppm)
157.8
155.3
135.8
133.4
130.1
129.9
127.9
121.1
115.1
111.5
103.3
55.3
33.8
26.8
19.7
f1 (ppm)

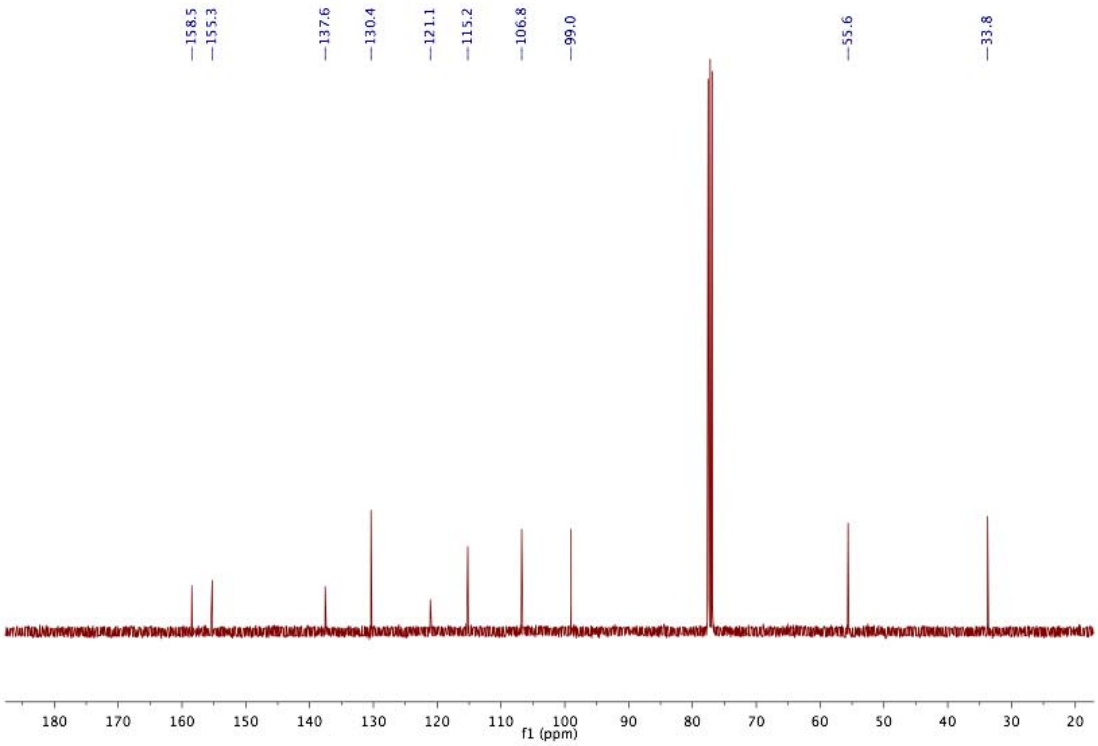

TBSO
7.13
7.10
7.08
6.46
6.42
6.06
5.98
5.30
5.25
4.51
4.50
4.49
4.48
0.98
0.20
1.09
1.00
2.13
1.07
1.09
1.09
2.12
8.79
5.63
f1 (ppm)
159.9
157.0
133.6
129.9
117.8
113.0
107.9
107.4
69.0
25.9
18.4
-4.2
f1 (ppm)

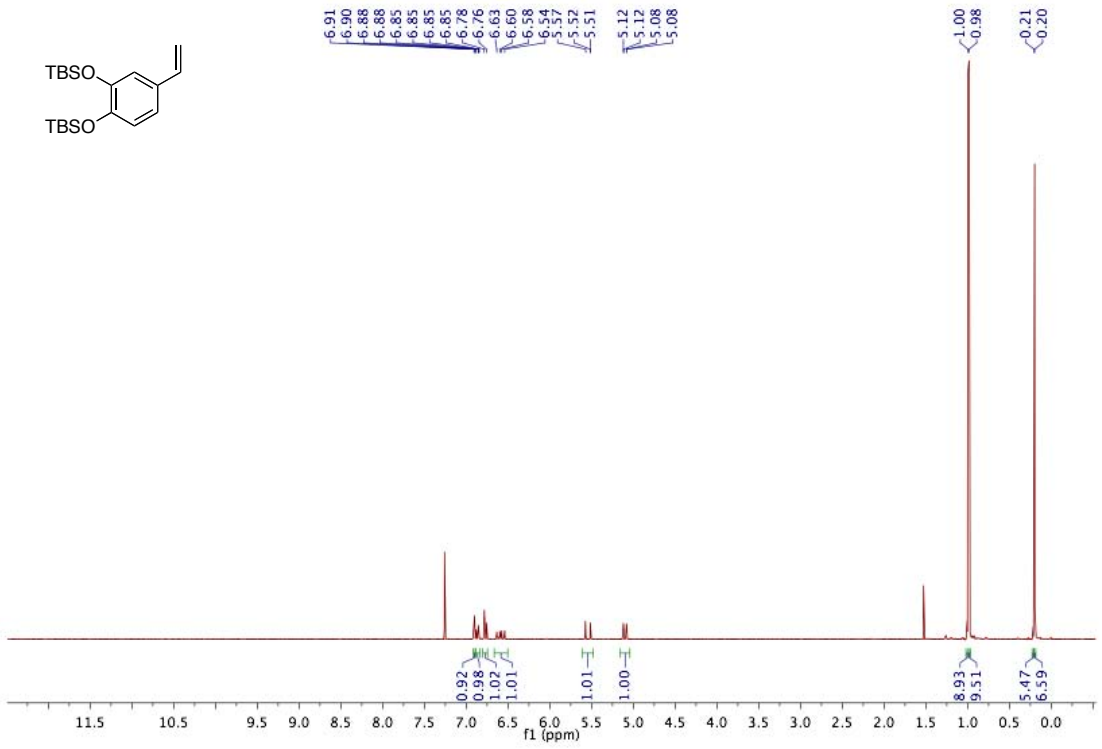

OH
TBSO
6.93
6.91
6.37
6.34
6.05
5.99
5.13
5.11
4.86
3.35
3.33
0.97
0.19
0.99
0.98
0.93
1.00
1.05
0.95
0.97
2.10
9.30
6.01
f1 (ppm)
155.7
155.0
137.0
130.9
118.1
116.5
112.9
108.2
34.9
25.9
18.4
4.2
f1 (ppm)

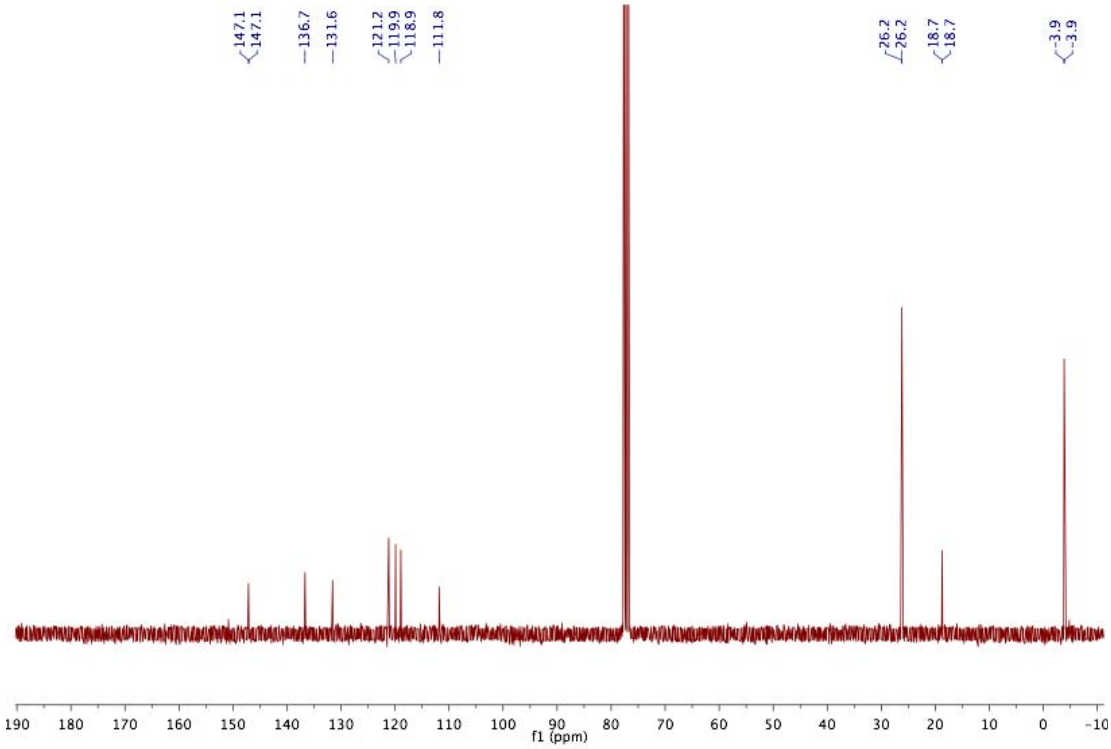

OMe
TBSO
6.96
6.96
6.93
6.93
6.37
6.02
5.96
5.90
5.04
5.02
4.99
4.99
4.98
3.78
3.31
3.29
0.99
0.20
1.00
1.95
1.01
0.98
0.96
3.09
2.09
9.07
5.89
f1 (ppm)

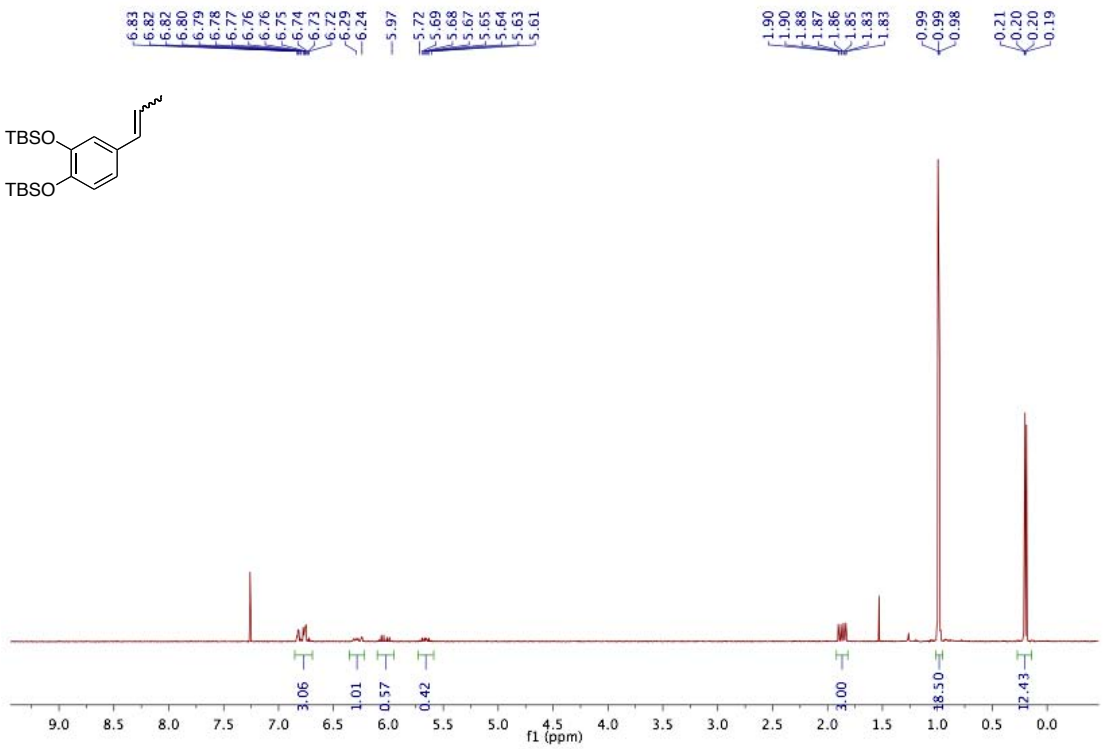

158.2
155.3
137.7
130.0
121.5
115.1
111.6
103.7
55.6
33.8
26.0
18.4
-4.2
f1 (ppm)

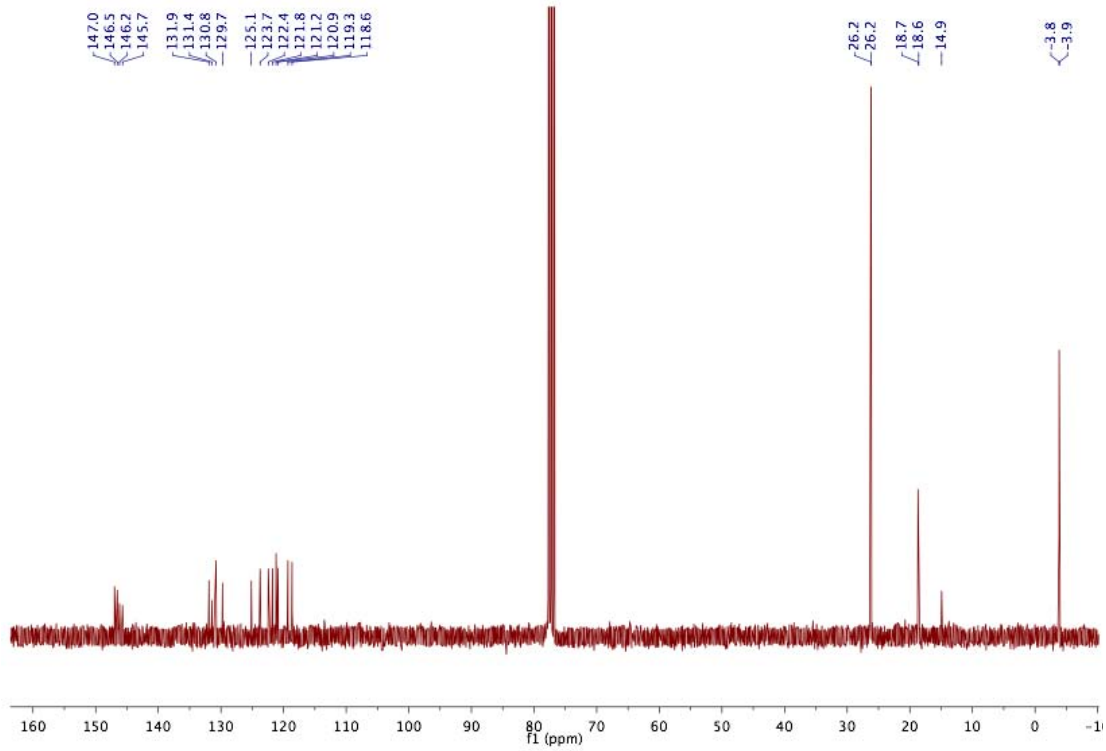

OMe
HO
6.97
6.95
6.36
6.34
5.99
5.95
5.91
5.00
4.99
4.99
4.61
3.79
3.30
3.30
3.30
3.29
3.29
3.29
3.28
3.28
1.03
1.01
0.99
1.00
1.04
0.95
0.92
3.24
2.17
f1 (ppm)

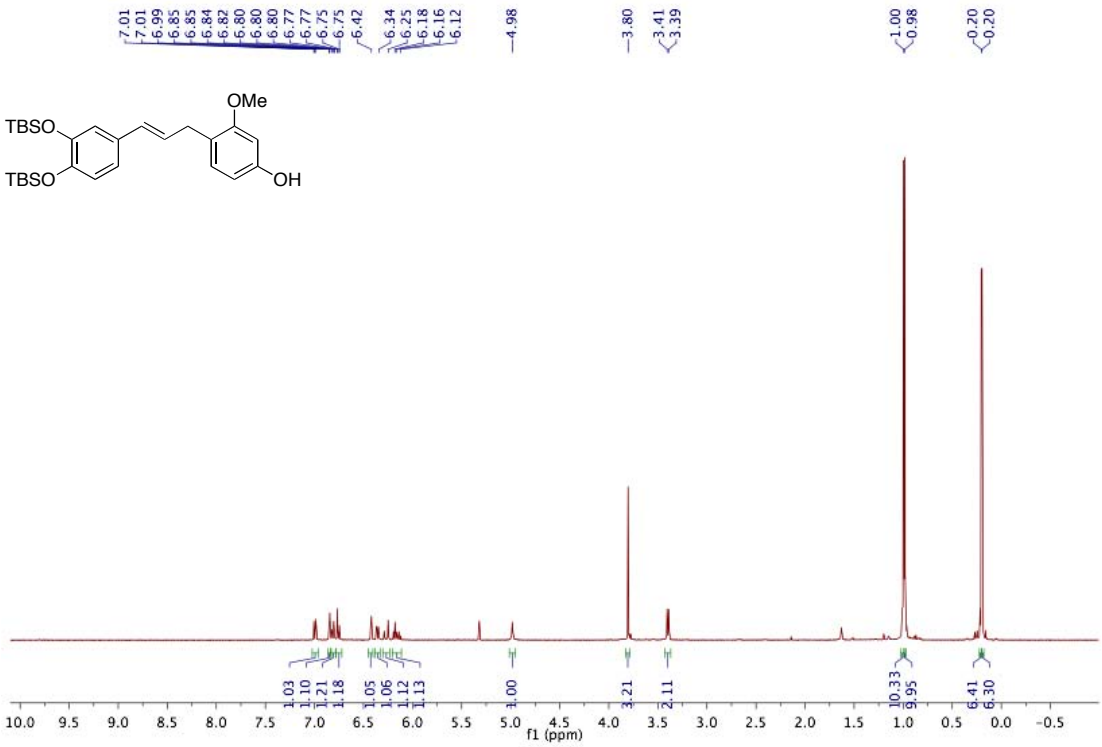

158.5
155.3
137.6
130.4
121.1
115.2
106.8
99.0
55.6
33.8
f1 (ppm)

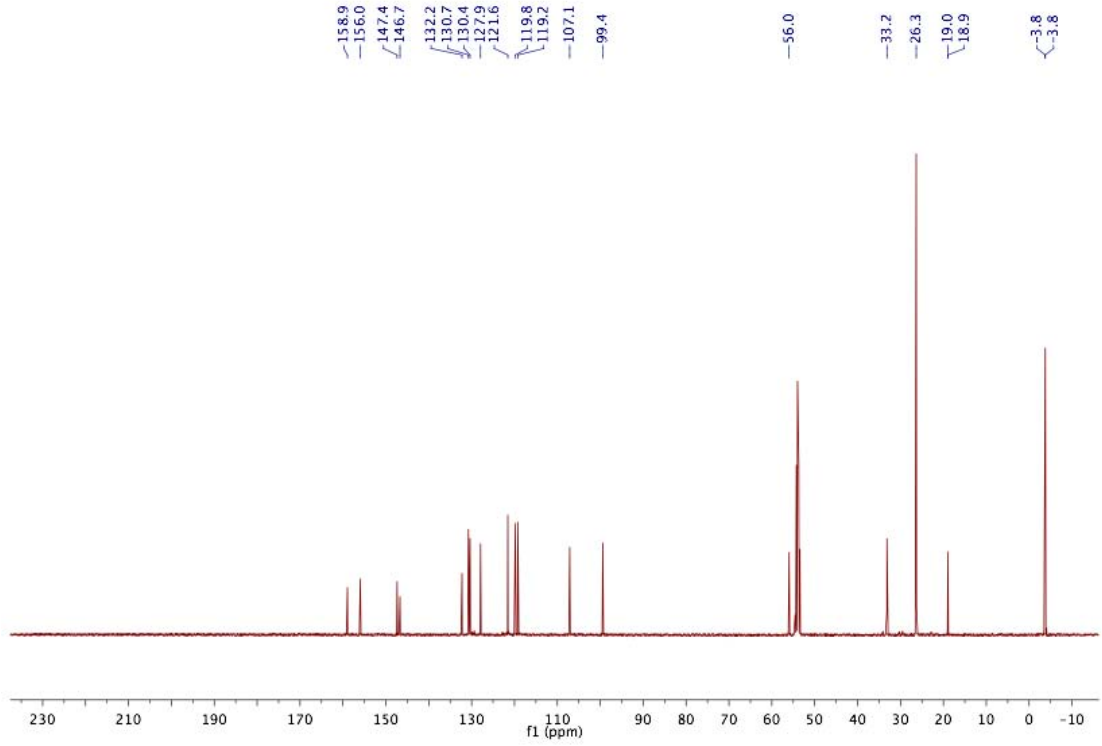

TBSO
TBSO
6.91
6.90
6.88
6.88
6.85
6.85
6.85
6.85
6.78
6.76
6.63
6.60
6.58
6.54
5.57
5.52
5.51
5.12
5.12
5.08
5.08
1.00
0.98
0.21
0.20
0.92
0.98
1.02
1.01
1.01
1.00
8.93
9.51
5.47
6.59
f1 (ppm)

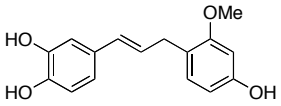

147.1
147.1
136.7
131.6
121.2
119.9
118.9
111.8
26.2
26.2
18.7
18.7
-3.9
-3.9
f1 (ppm)


6.83
6.82
6.82
6.80
6.79
6.78
6.77
6.76
6.76
6.75
6.74
6.73
6.72
6.29
6.24
5.97
5.72
5.69
5.68
5.67
5.65
5.64
5.63
5.61
1.90
1.90
1.88
1.87
1.86
1.85
1.83
1.83
0.99
0.99
0.98
0.21
0.20
0.20
0.19
TBSO
TBSO
3.06
1.01
0.57
0.42
3.00
18.50
12.43
f1 (ppm)

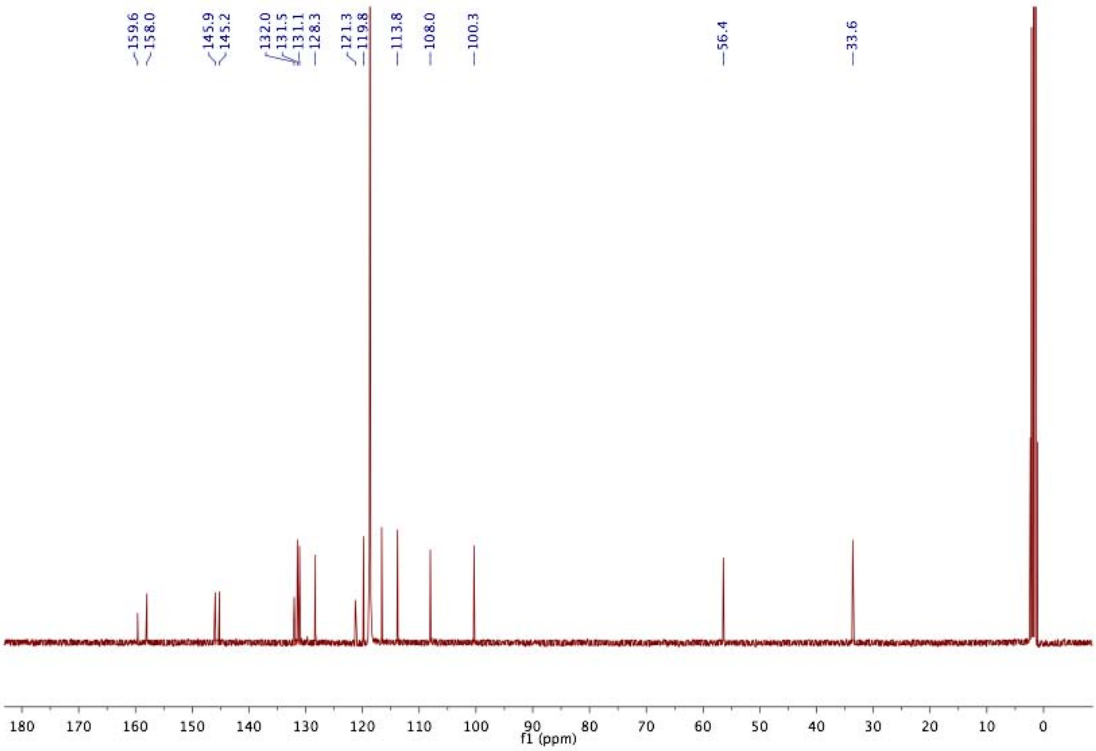

147.0
146.5
146.2
145.7
131.9
131.4
130.8
129.7
125.1
123.7
122.4
121.8
121.2
120.9
119.3
118.6
26.2
26.2
18.7
18.6
14.9
-3.8
-3.9
f1 (ppm)

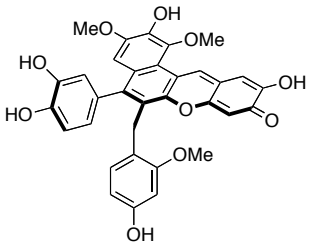

7.01
7.01
6.99
6.85
6.85
6.84
6.82
6.80
6.80
6.80
6.77
6.77
6.75
6.75
6.42
6.34
6.25
6.18
6.16
6.12
4.98
3.80
3.41
3.39
1.00
0.98
0.20
0.20
OMe
TBSO
TBSO
OH
1.03
1.10
1.21
1.18
1.05
1.06
1.12
1.13
1.00
3.21
2.11
10.33
9.95
6.41
6.30
f1 (ppm)


158.9
156.0
147.4
146.7
132.2
130.7
130.4
127.9
121.6
119.8
119.2
107.1
99.4
56.0
33.2
26.3
19.0
18.9
-3.8
-3.8
f1 (ppm)

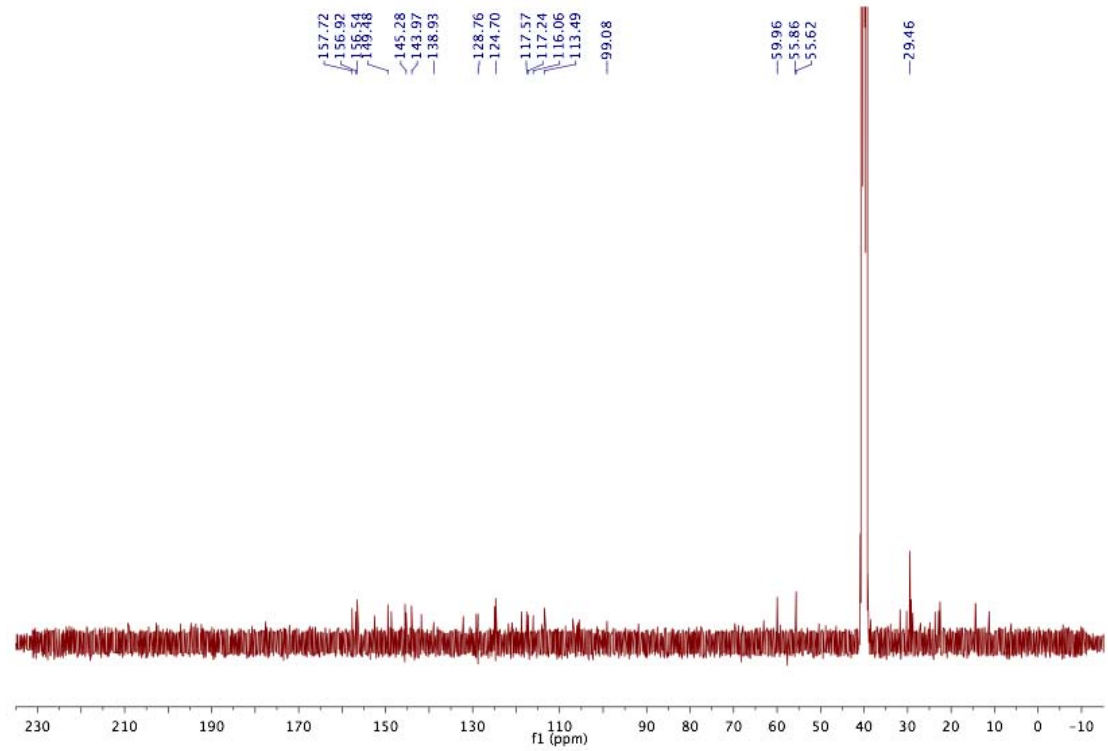

HO
HO
OMe
OH

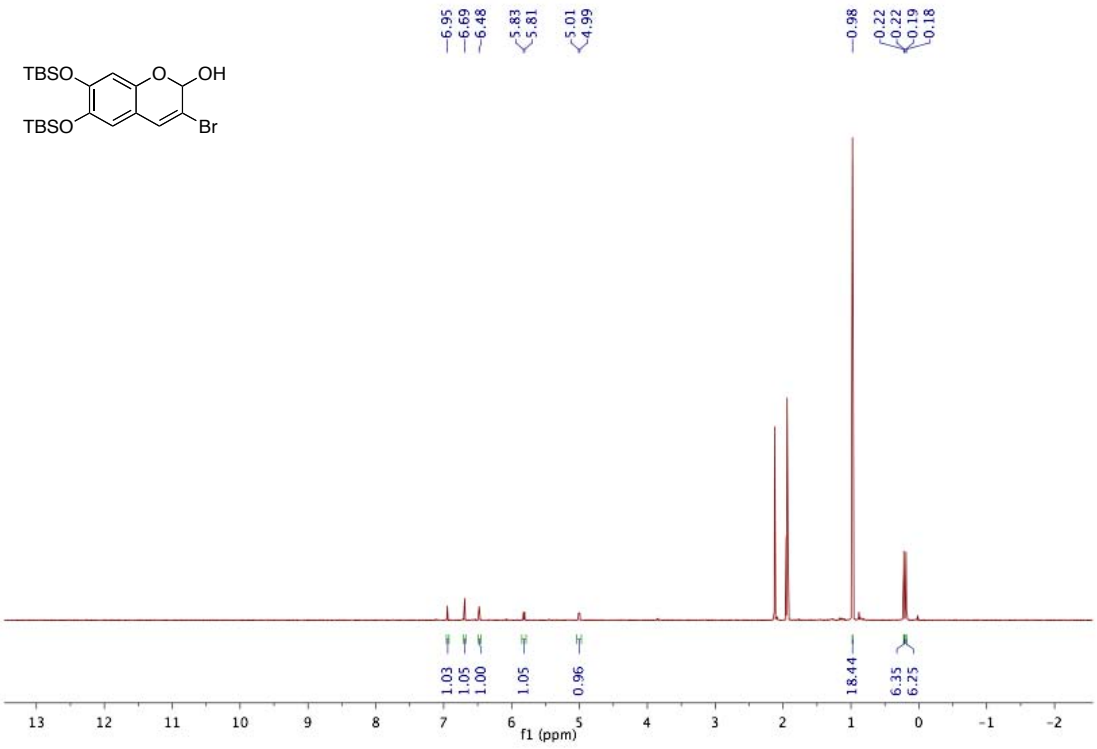
6.96
6.94
6.84
6.71
6.43
6.27
6.23
6.18
6.16
6.15
6.14
6.12
6.11
3.78
3.35
3.33
0.91
1.01
2.10
0.93
0.97
0.96
1.00
2.93
1.87
f1 (ppm)

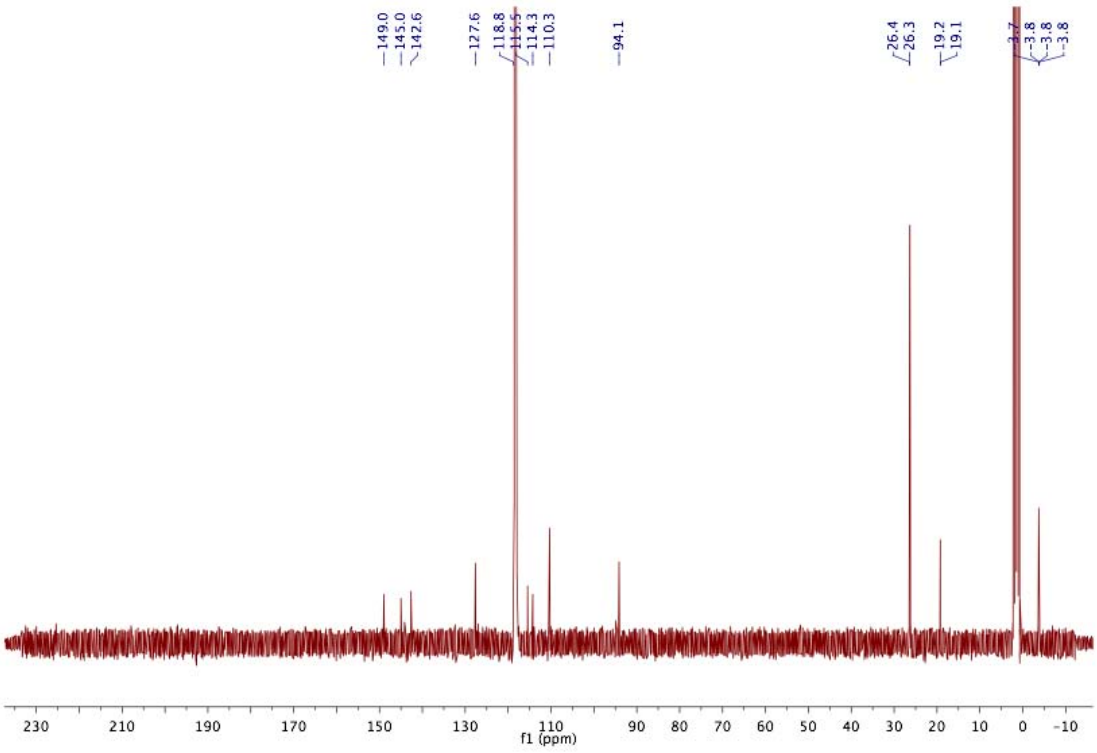

159.6
158.0
145.9
145.2
132.0
131.5
131.1
128.3
121.3
119.8
113.8
108.0
100.3
56.4
33.6
f1 (ppm)

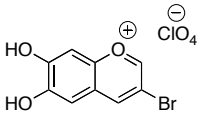


Santalin Y benzoxanthone isomere

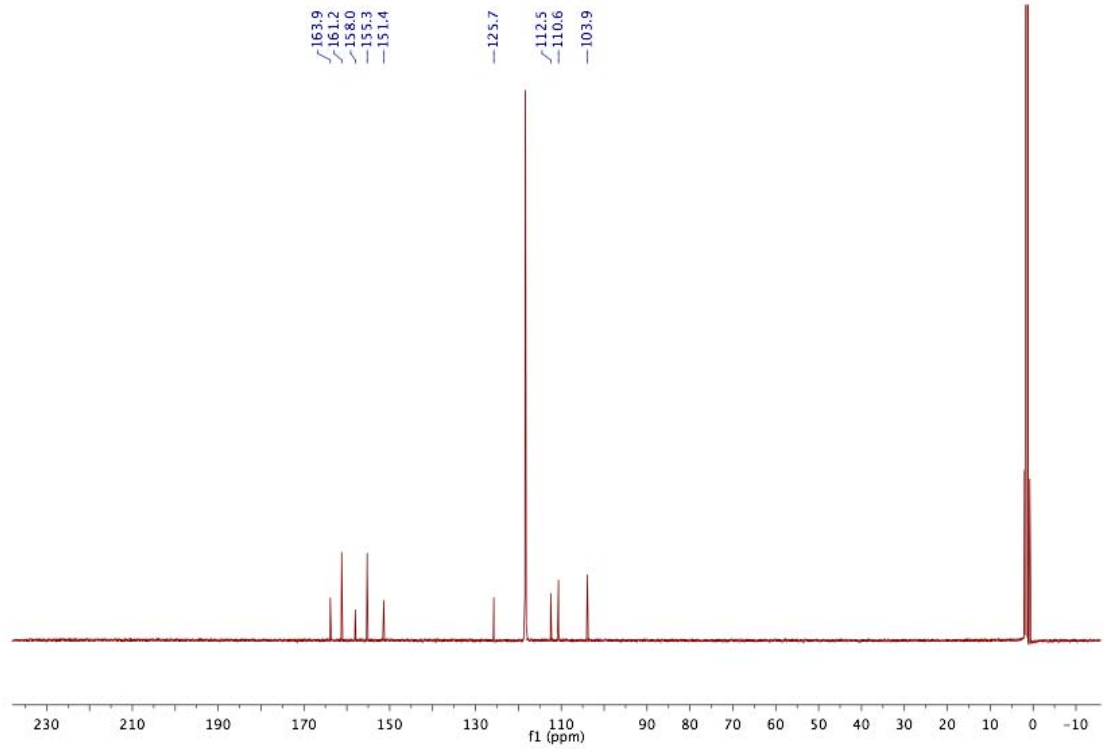


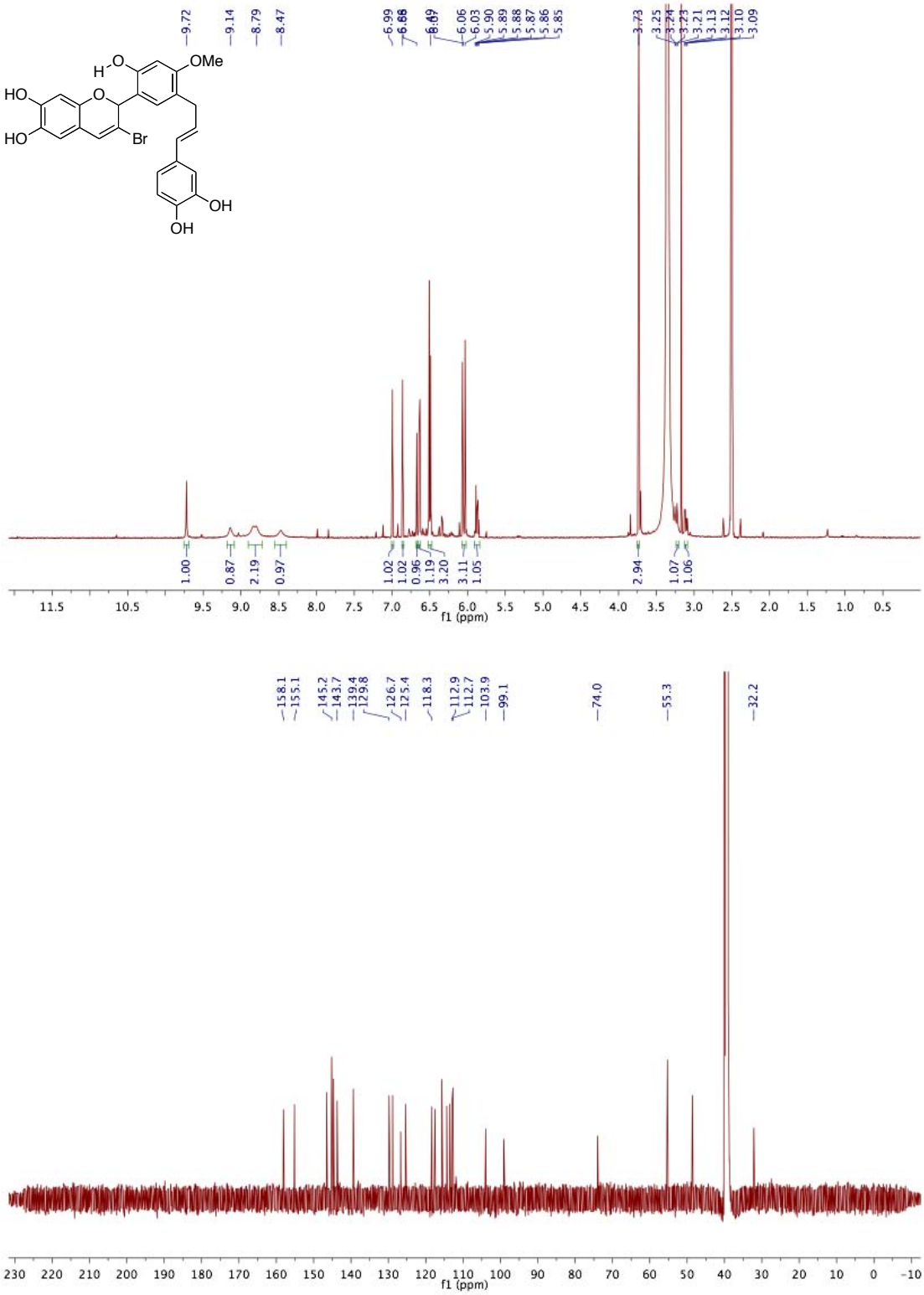

TBSO
TBSO
O
OH
Br
6.95
6.69
6.48
5.83
5.81
5.01
4.99
0.98
0.22
0.22
0.19
0.18
1.03
1.05
1.00
1.05
0.96
18.44
6.35
6.25
f1 (ppm)

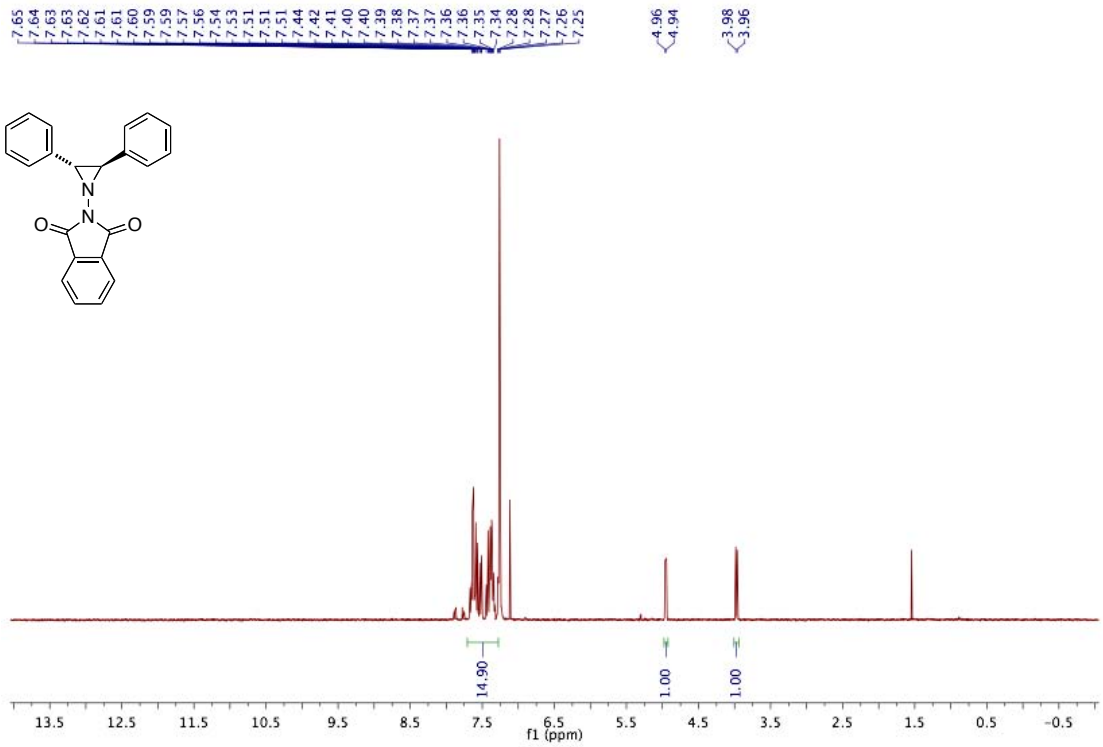

149.0
145.0
142.6
127.6
118.8
115.5
114.3
110.3
94.1
26.4
26.3
19.2
19.1
3.7
-3.8
-3.8
-3.8
f1 (ppm)

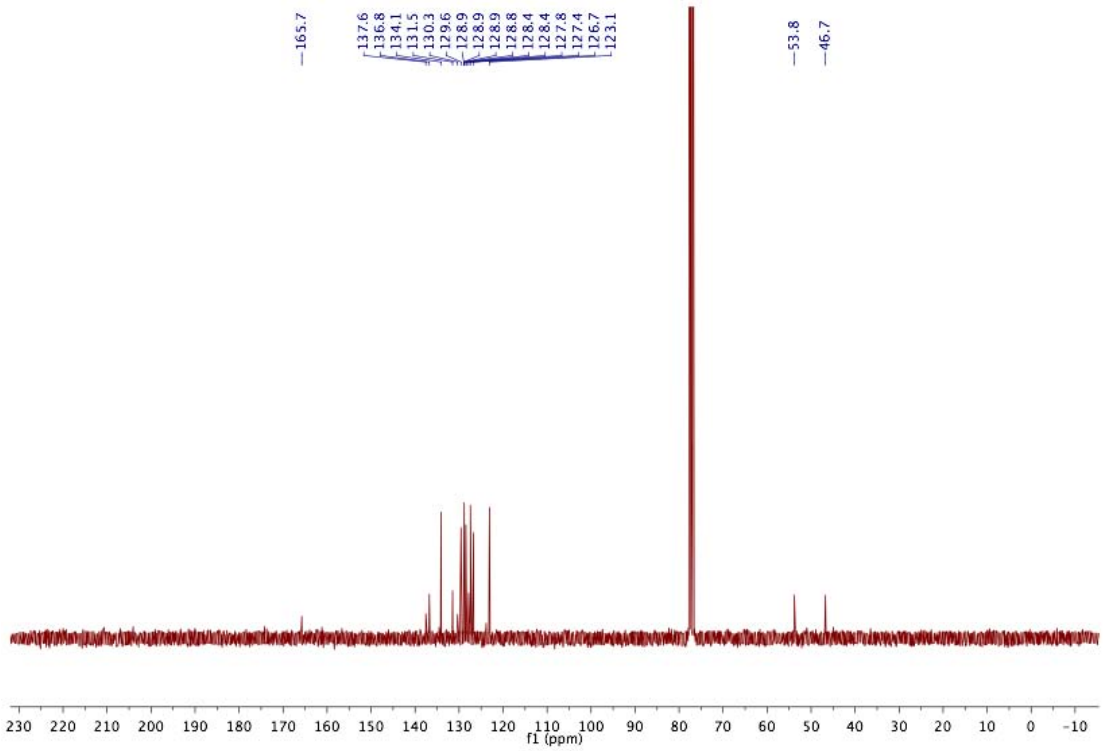

HO
HO
O
Br
ClO4

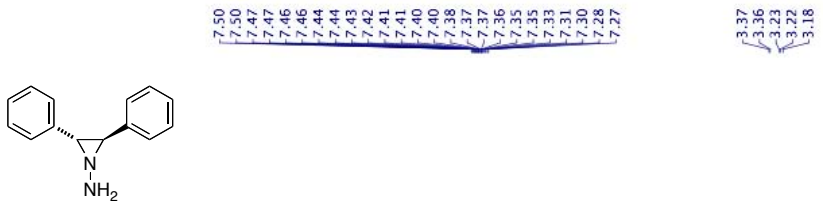
10.16
9.31
9.25
9.25
9.25
9.25
9.06
7.61
7.61
7.54
7.54
0.67
1.00
1.10
0.87
1.08
1.05
f1 (ppm)


163.9
161.2
158.0
155.3
151.4
125.7
112.5
110.6
103.9
f1 (ppm)

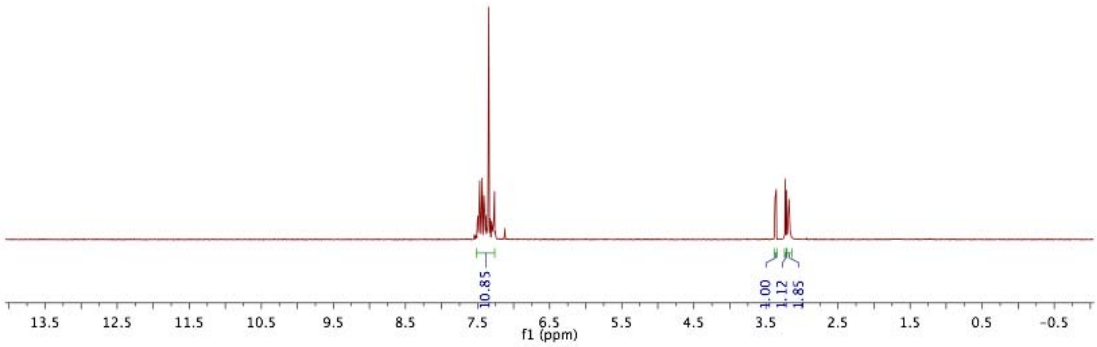

HO
HO
O
H
O
OMe
Br
OH
OH
9.72
9.14
8.79
8.47
6.99
6.66
6.49
6.06
6.03
5.90
5.89
5.88
5.87
5.86
5.85
3.73
3.25
3.24
3.23
3.21
3.13
3.12
3.10
3.09
1.00
0.87
2.19
0.97
1.02
1.02
0.96
1.19
3.20
3.11
1.05
2.94
1.07
1.06
f1 (ppm)
158.1
155.1
145.2
143.7
139.4
129.8
126.7
125.4
118.3
112.9
112.7
103.9
99.1
74.0
55.3
32.2
f1 (ppm)

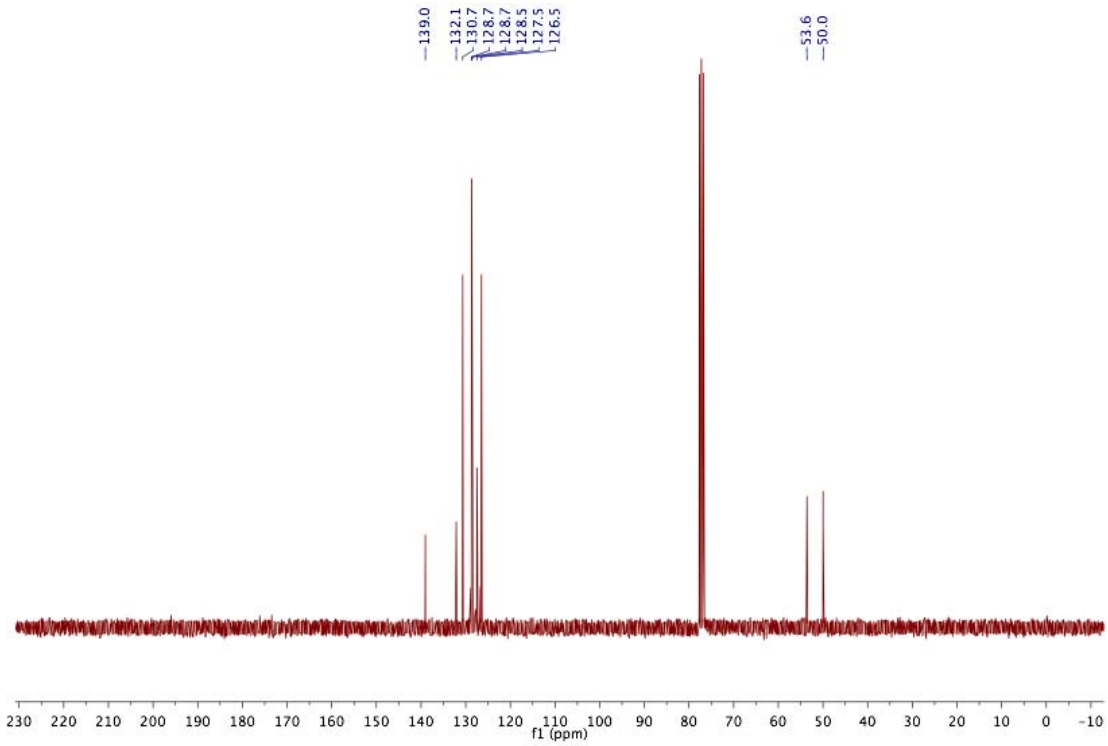

7.65
7.64
7.63
7.63
7.62
7.61
7.61
7.60
7.59
7.59
7.57
7.56
7.54
7.53
7.51
7.51
7.51
7.44
7.42
7.41
7.40
7.40
7.39
7.38
7.37
7.37
7.36
7.36
7.35
7.34
7.28
7.28
7.27
7.26
7.25
4.96
4.94
3.98
3.96
O
N
N
O
14.90
1.00
1.00
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

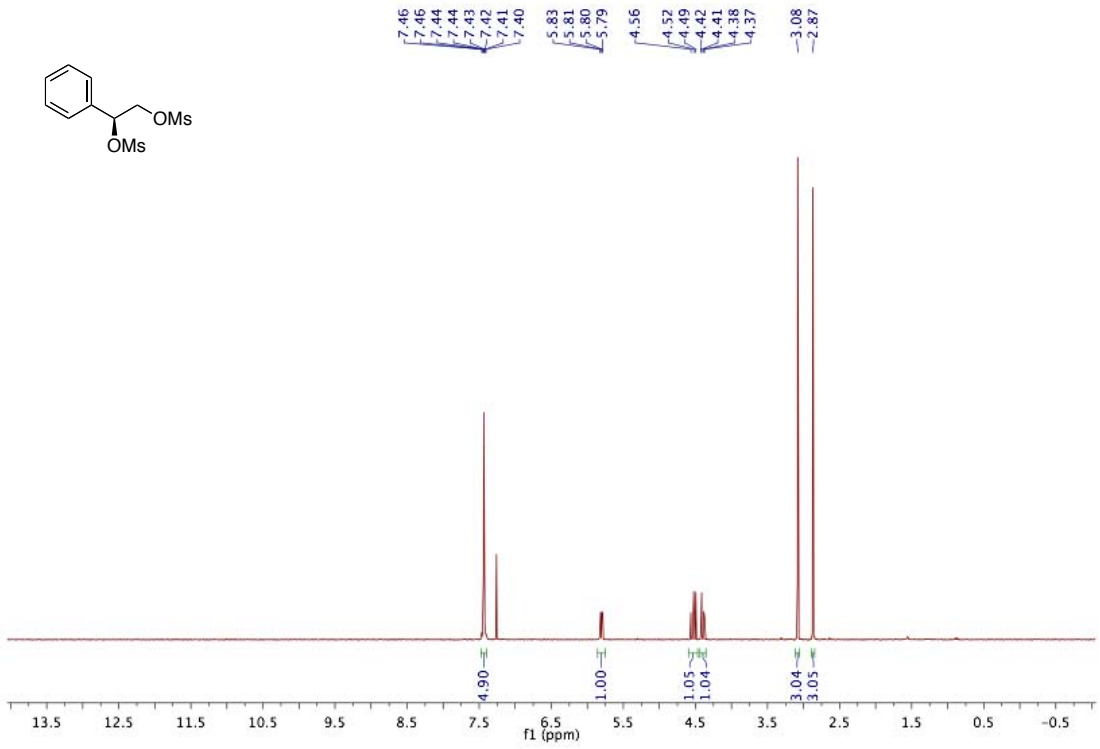

165.7
137.6
136.8
134.1
131.5
130.3
129.6
128.9
128.9
128.9
128.8
128.4
128.4
127.8
127.4
126.7
123.1
53.8
46.7
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

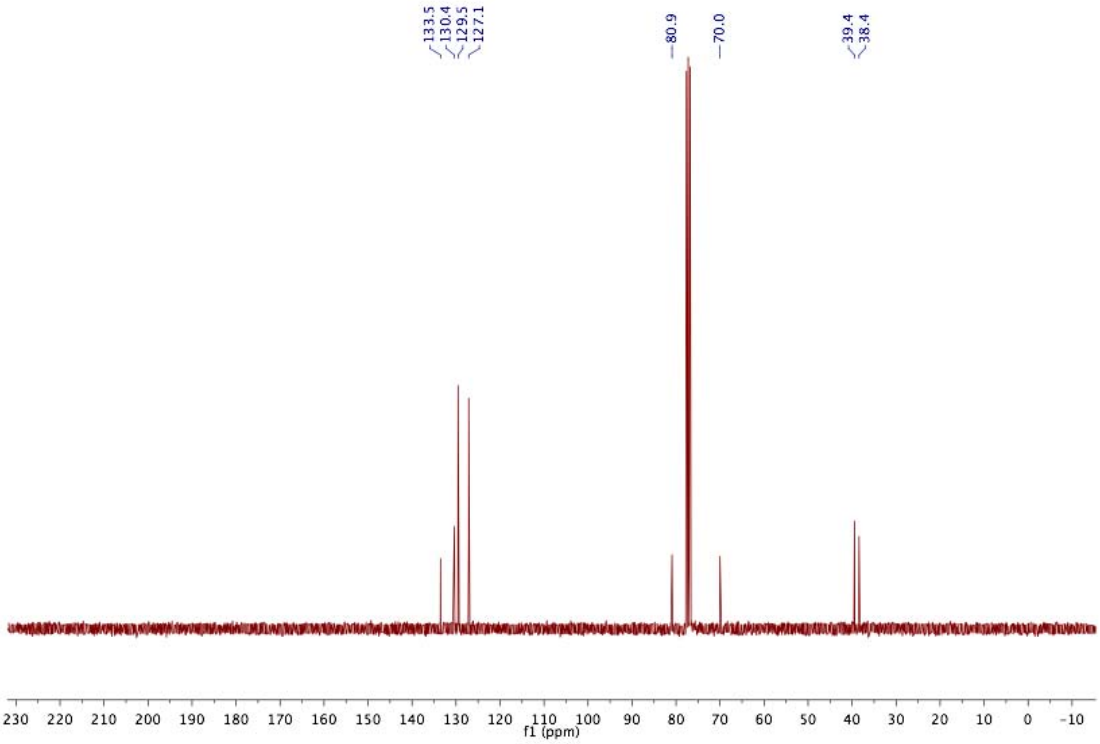

7.50
7.50
7.47
7.47
7.46
7.46
7.44
7.44
7.43
7.42
7.41
7.41
7.40
7.40
7.38
7.37
7.37
7.36
7.35
7.35
7.33
7.31
7.30
7.28
7.27
3.37
3.36
3.23
3.22
3.18

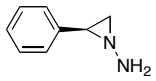
N
NH2


10.85
3.00
1.12
1.85
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

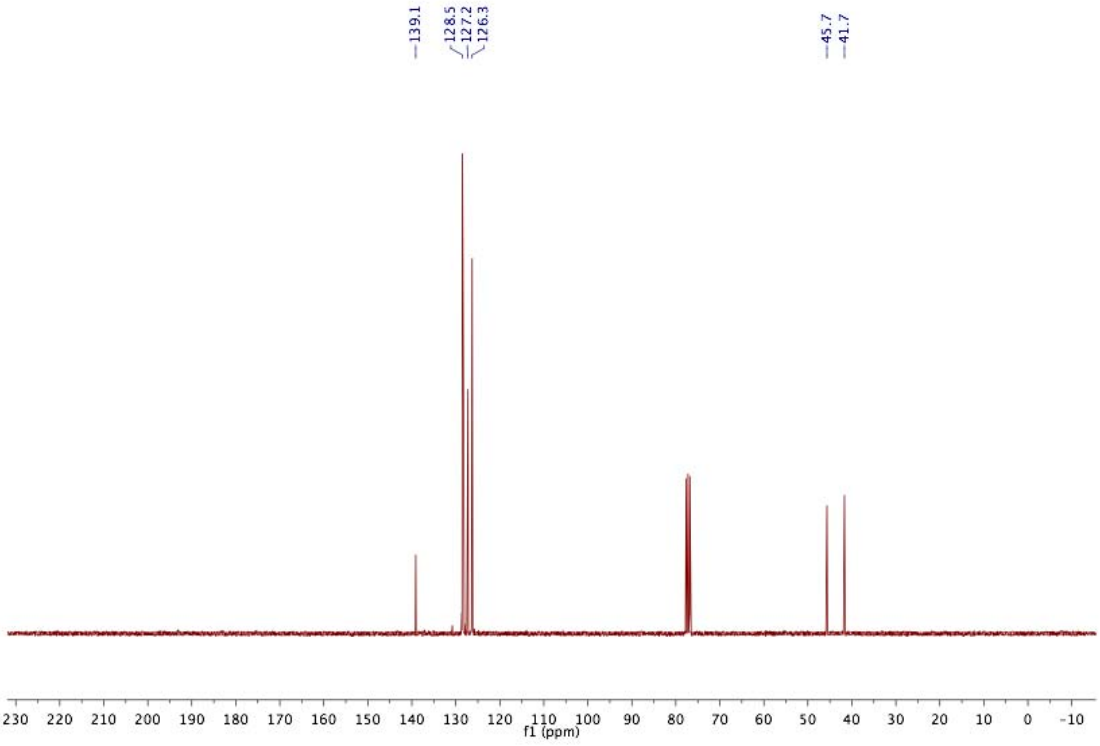

139.0
132.1
130.7
128.7
128.7
128.5
127.5
126.5
53.6
50.0
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

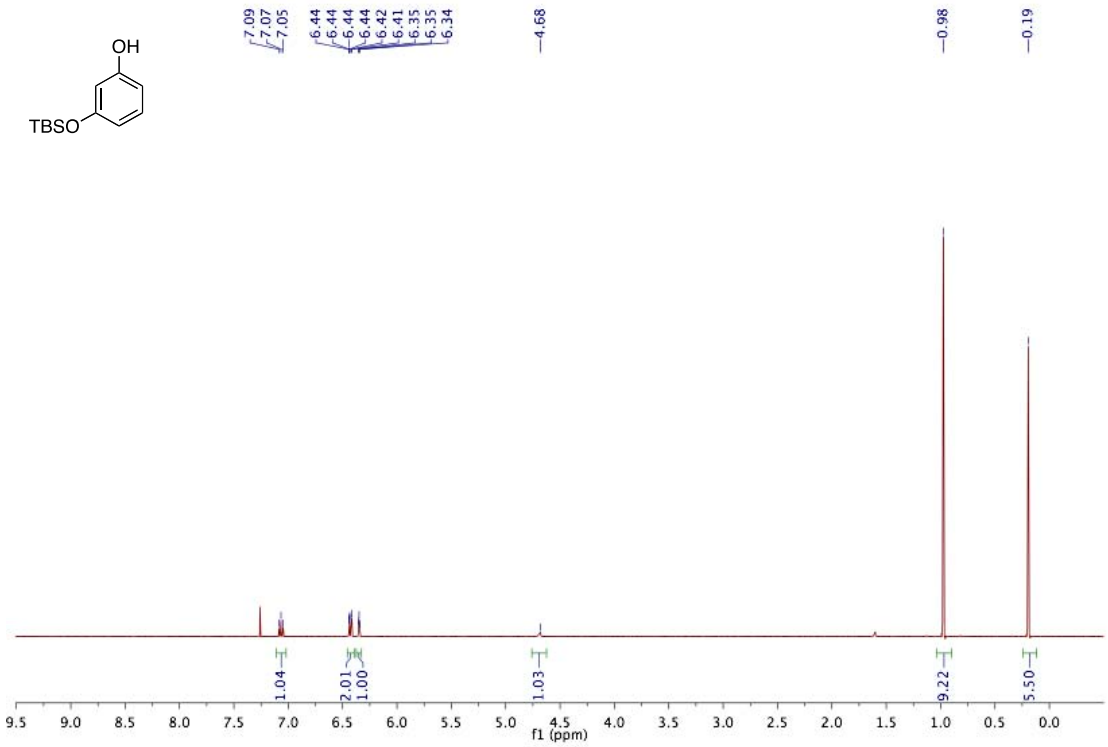

OMs
OMs
7.46
7.46
7.44
7.44
7.43
7.42
7.41
7.40
5.83
5.81
5.80
5.79
4.56
4.52
4.49
4.42
4.41
4.38
4.37
3.08
2.87
4.90
1.00
1.05
1.04
3.04
3.05
f1 (ppm)

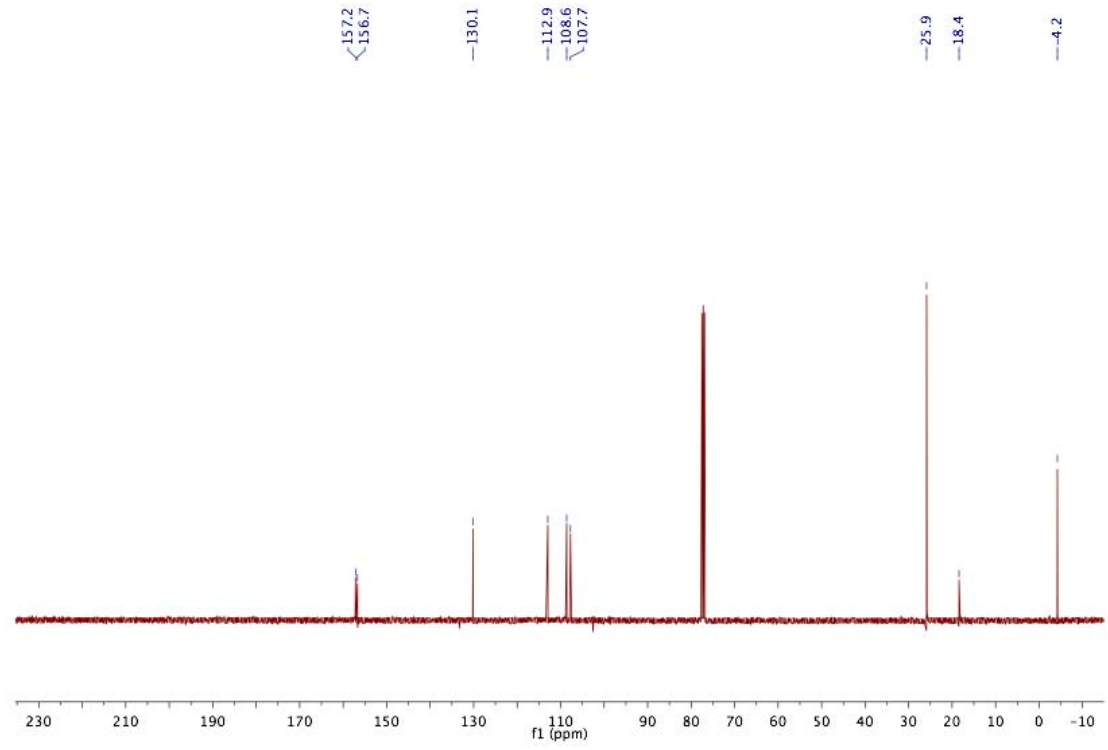

133.5
130.4
129.5
127.1
80.9
70.0
39.4
38.4
f1 (ppm)

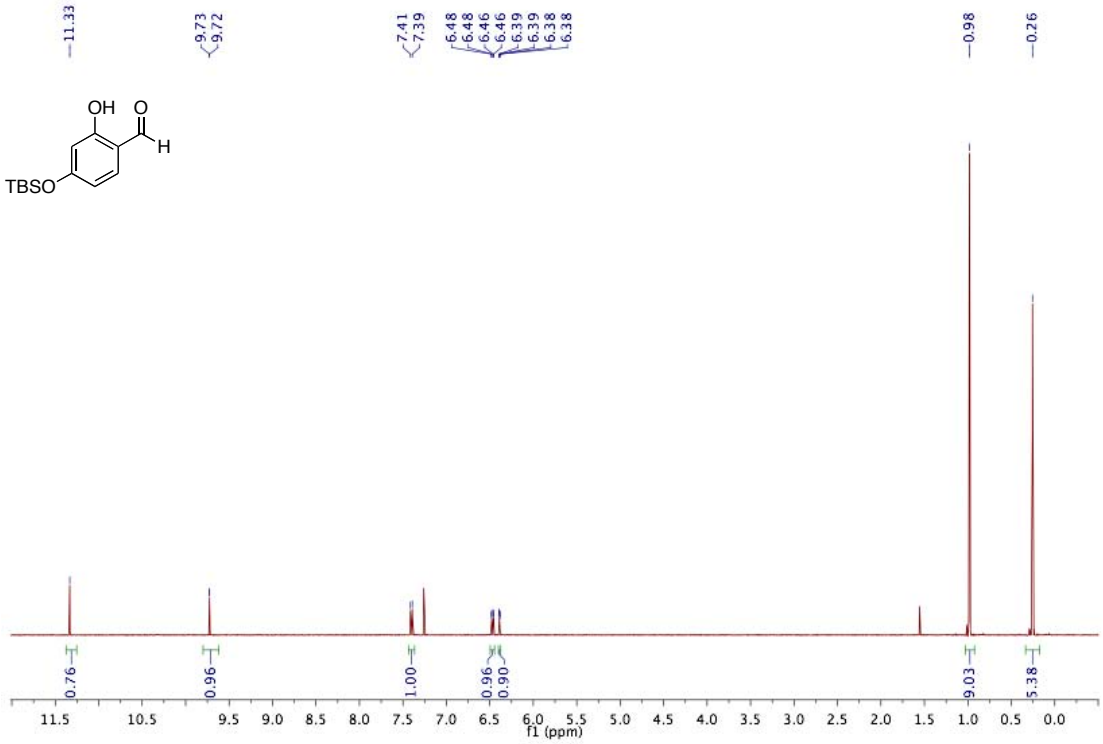

N
NH2

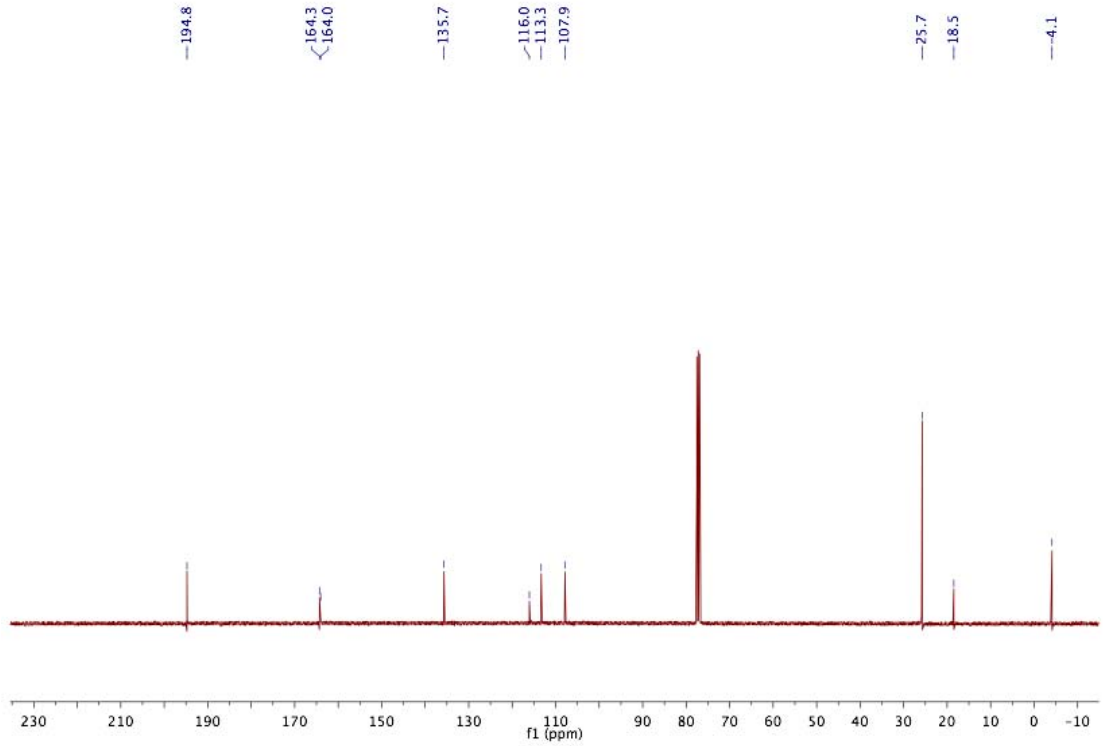
7.33
7.33
7.30
7.30
7.28
7.28
7.28
7.26
7.26
7.26
7.25
7.23
7.20
7.19
7.18
7.17
7.17
7.17
7.16
3.59
2.62
2.61
2.59
2.05
2.05
2.04
2.04
2.02
2.02
2.00
2.00
4.96
2.16
1.00
1.03
1.09
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

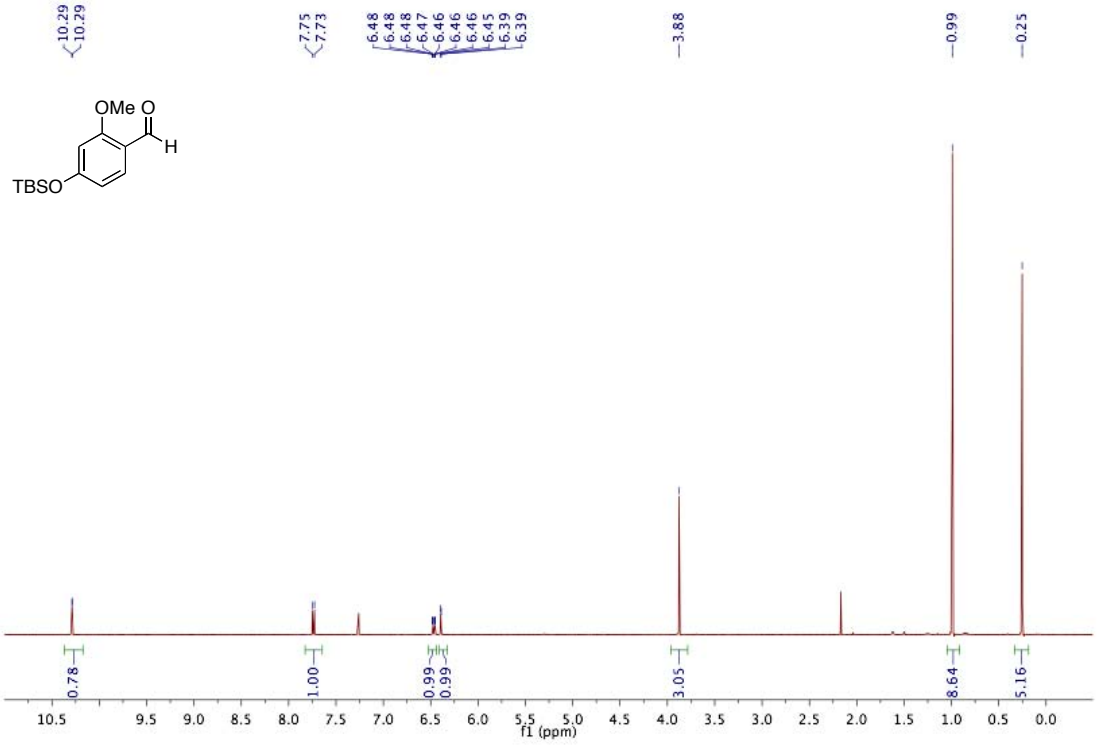

139.1
128.5
127.2
126.3
45.7
41.7
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

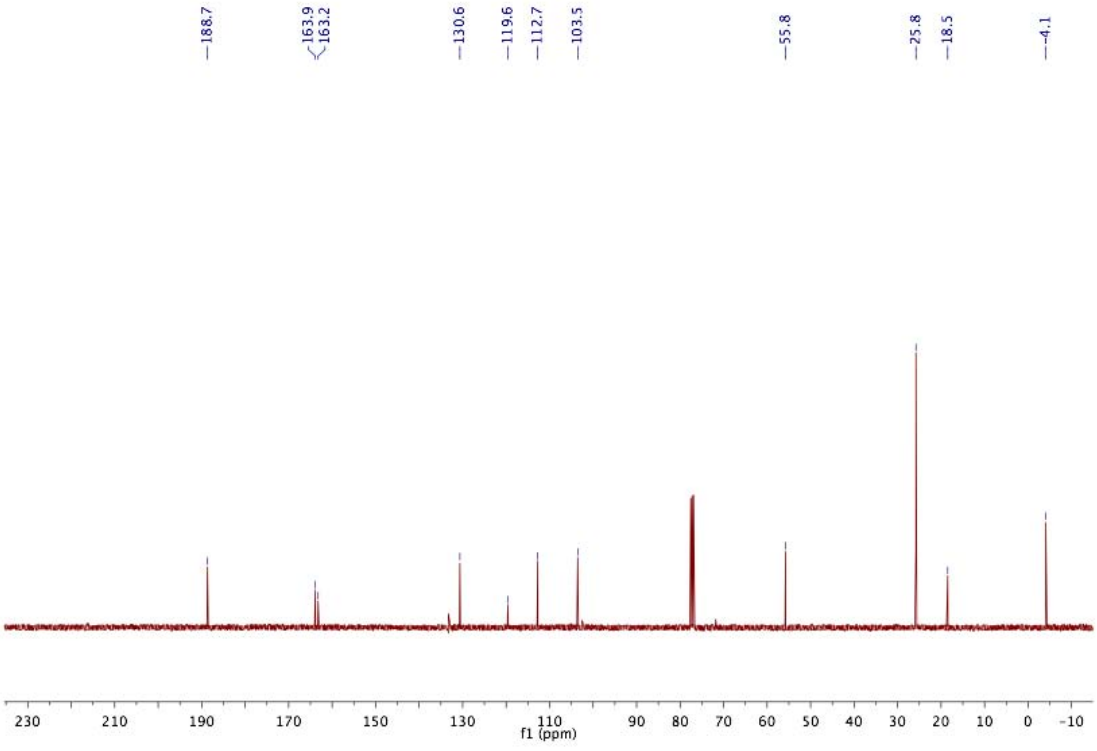

OH
TBSO
7.09
7.07
7.05
6.44
6.44
6.44
6.44
6.42
6.41
6.35
6.35
6.34
4.68
0.98
0.19
1.04
2.01
1.00
1.03
9.22
5.50
f1 (ppm)

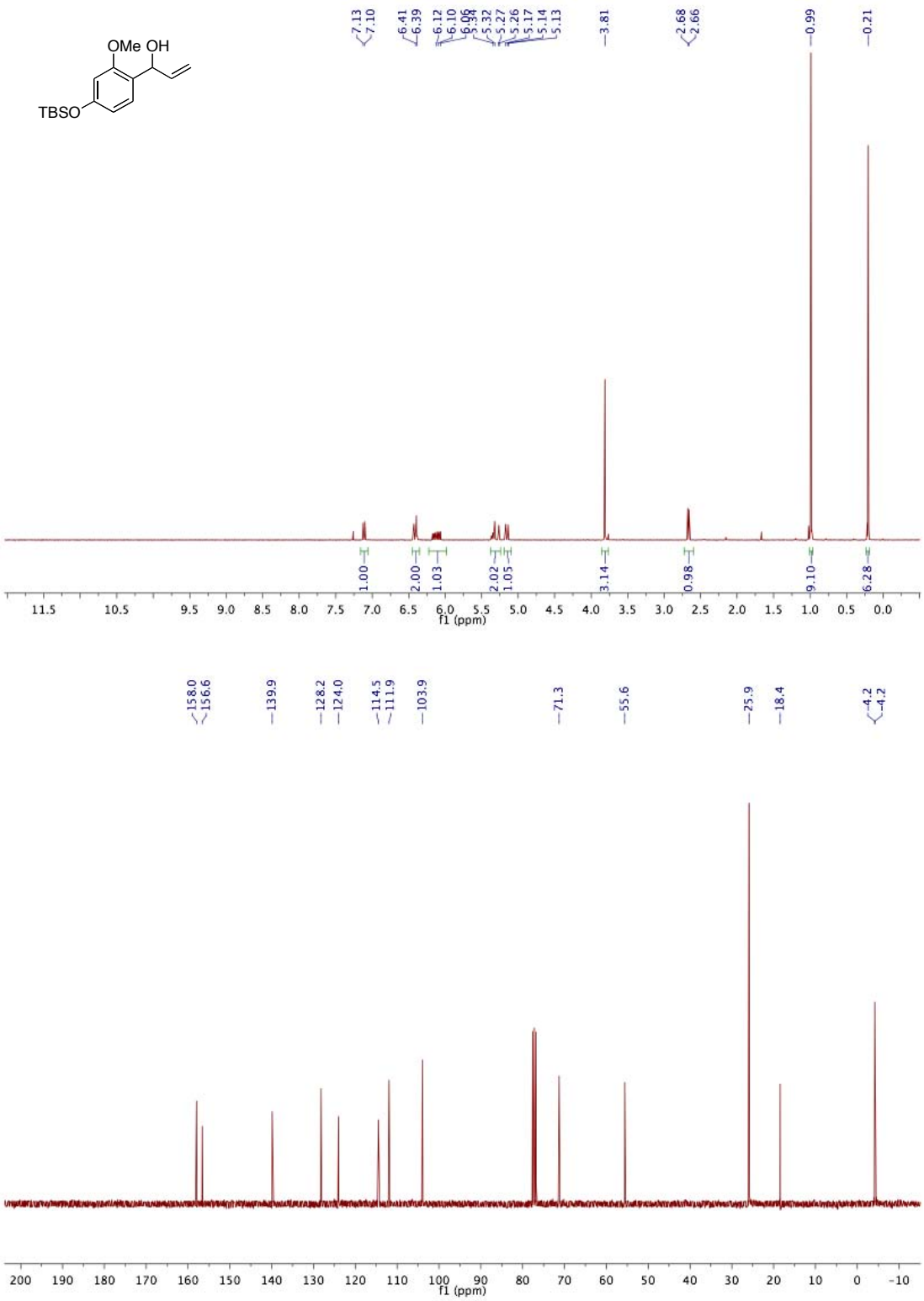

157.2
156.7
130.1
112.9
108.6
107.7
25.9
18.4
4.2
f1 (ppm)

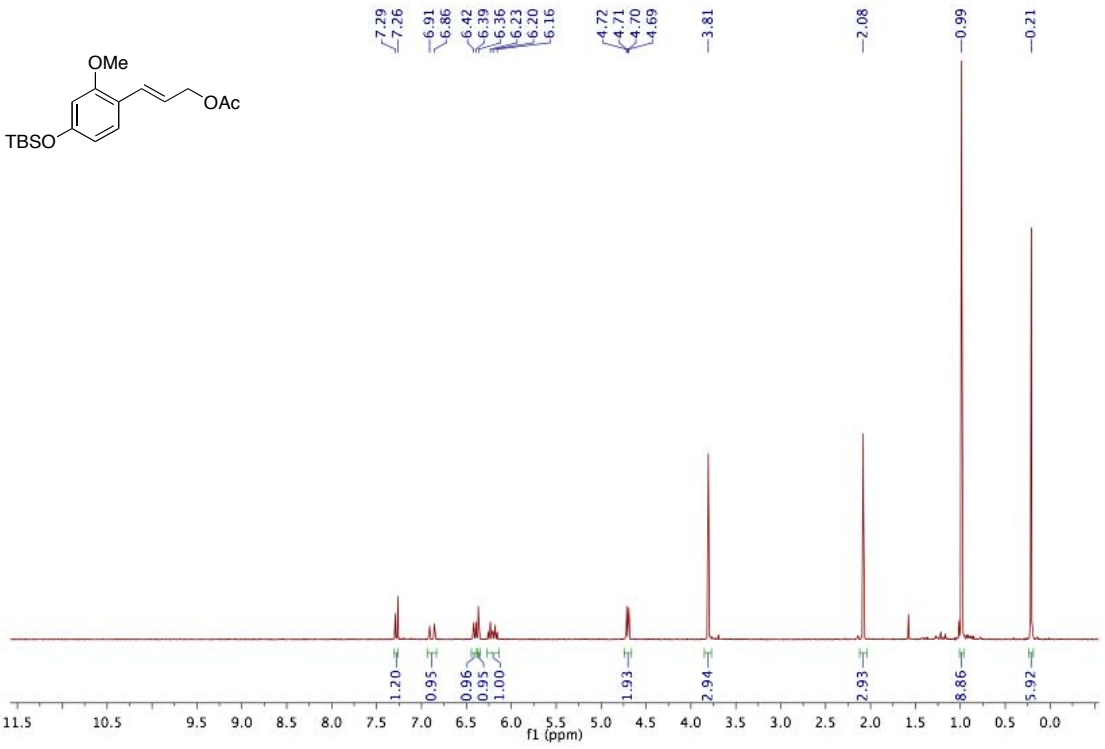

11.33
9.73
9.72
7.41
7.39
6.48
6.48
6.46
6.46
6.39
6.39
6.38
6.38
0.98
0.26
OH
O
H
TBSO
0.76
0.96
1.00
0.96
0.90
9.03
5.38
f1 (ppm)

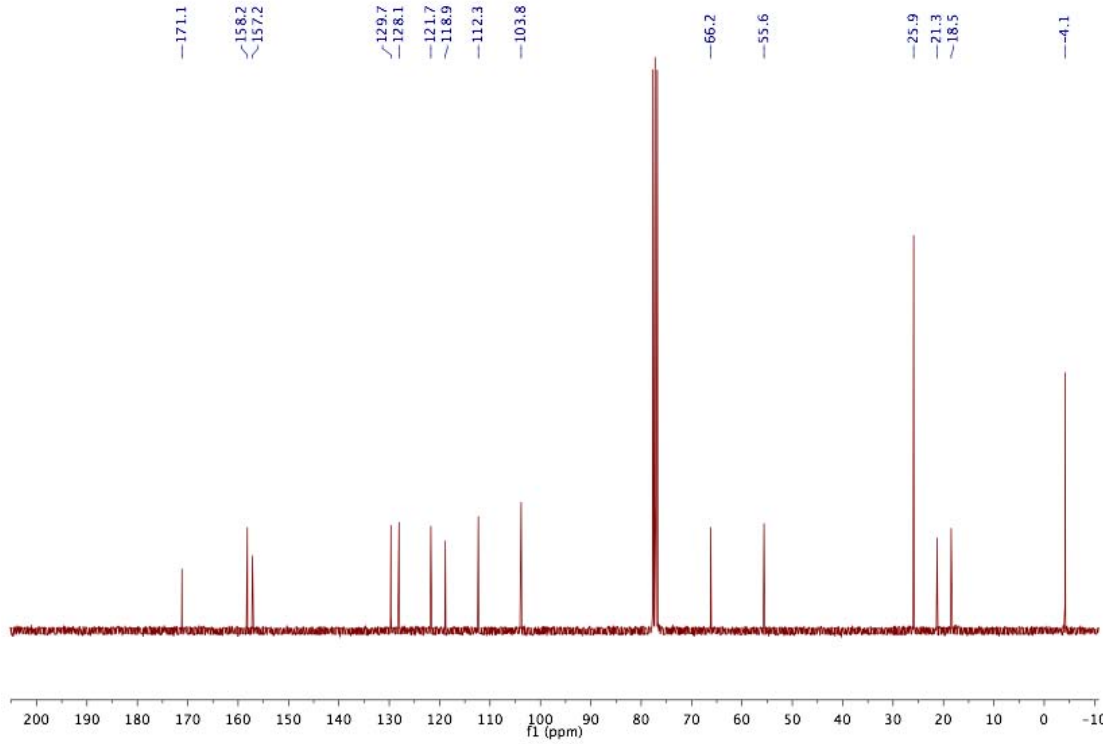

194.8
164.3
164.0
135.7
116.0
113.3
107.9
25.7
18.5
-4.1
f1 (ppm)

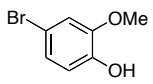

10.29
10.29
7.75
7.73
6.48
6.48
6.48
6.47
6.46
6.46
6.46
6.45
6.39
6.39
3.88
0.99
0.25
OMe O
H
TBSO
0.78
1.00
0.99
0.99
3.05
8.64
5.16
f1 (ppm)


188.7
163.9
163.2
130.6
119.6
112.7
103.5
55.8
25.8
18.5
-4.1
f1 (ppm)

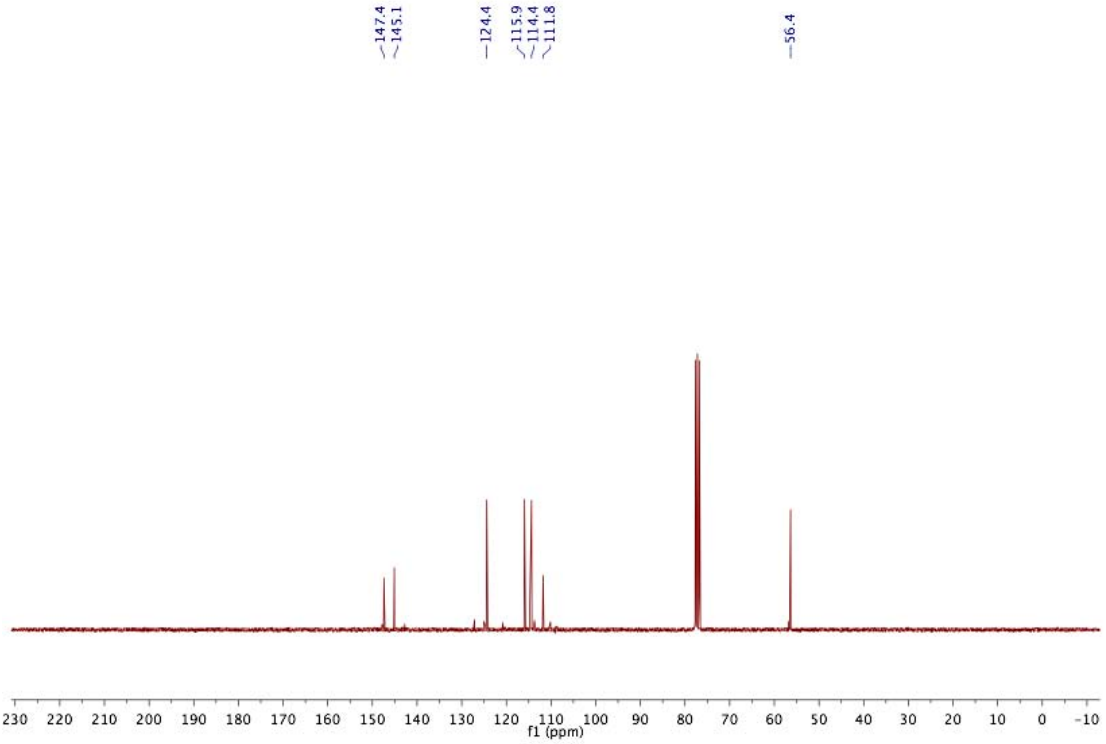

OMe OH
TBSO
7.13
7.10
6.41
6.39
6.12
6.10
5.32
5.27
5.26
5.17
5.14
5.13
3.81
2.68
2.66
0.99
0.21
1.00
2.00
1.03
2.02
1.05
3.14
0.98
9.10
6.28
f1 (ppm)
158.0
156.6
139.9
128.2
124.0
114.5
111.9
103.9
71.3
55.6
25.9
18.4
4.2
4.2
f1 (ppm)

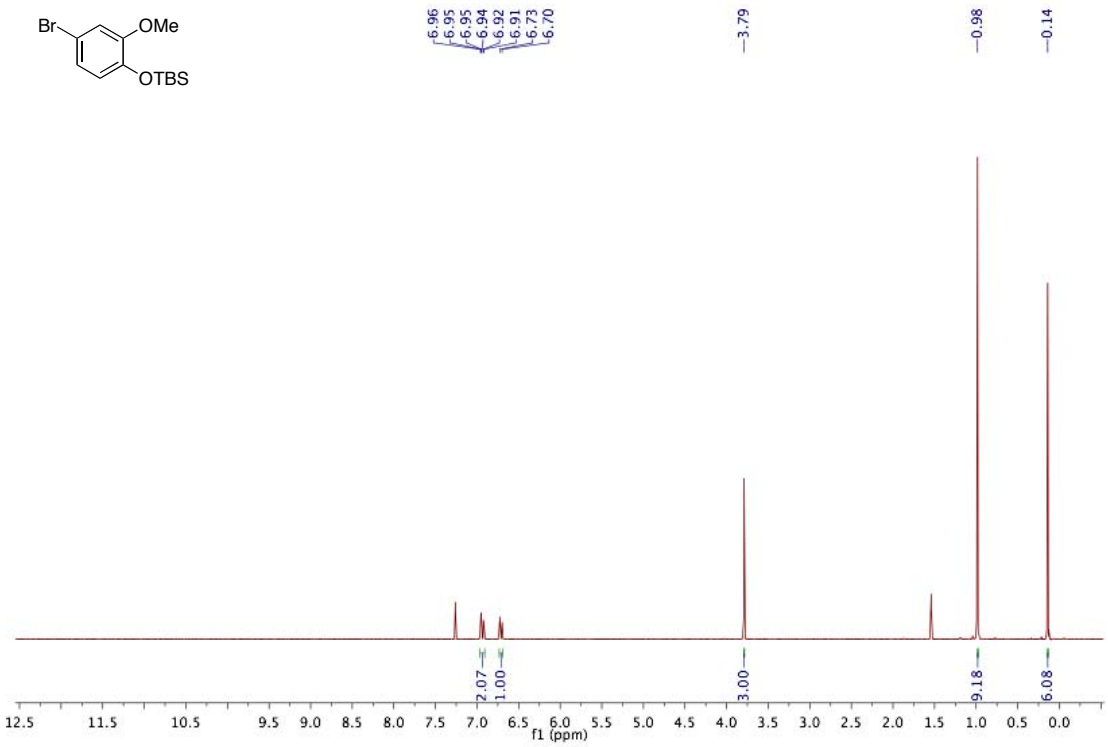

OMe
OAc
TBSO
7.29
7.26
6.91
6.86
6.42
6.39
6.36
6.23
6.20
6.16
4.72
4.71
4.70
4.69
3.81
2.08
0.99
0.21
1.20
0.95
0.96
0.95
1.00
1.93
2.94
2.93
8.86
5.92
f1 (ppm)

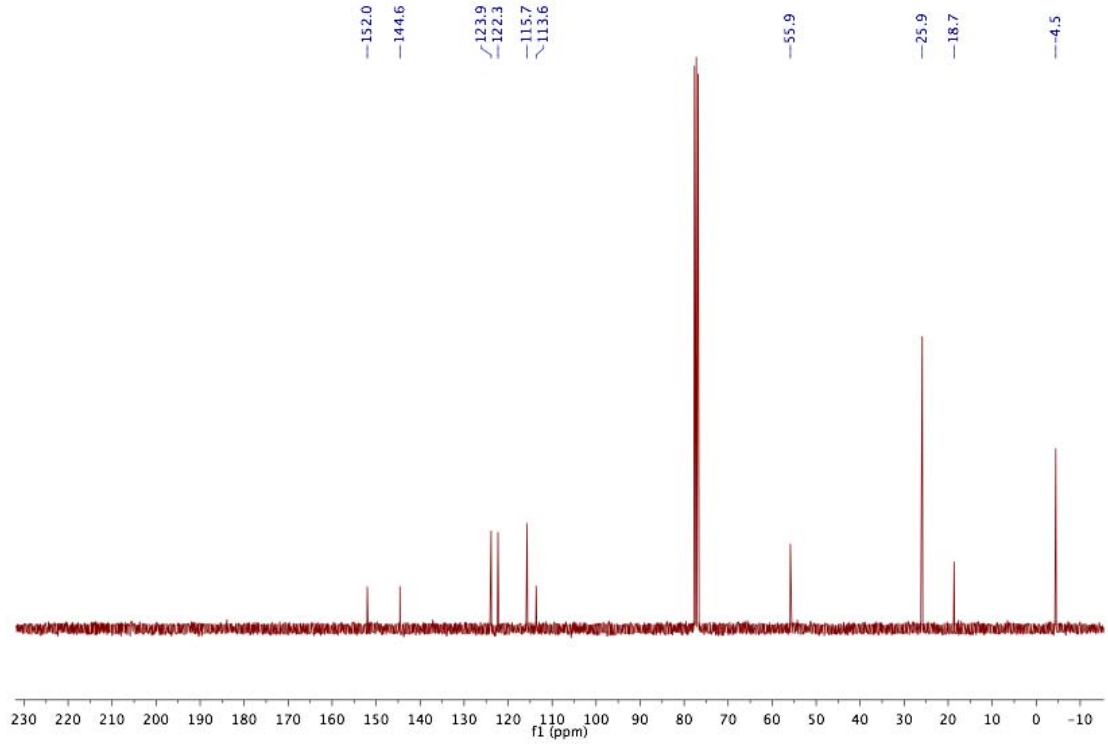

171.1
158.2
157.2
129.7
128.1
121.7
118.9
112.3
103.8
66.2
55.6
25.9
21.3
18.5
-4.1
f1 (ppm)

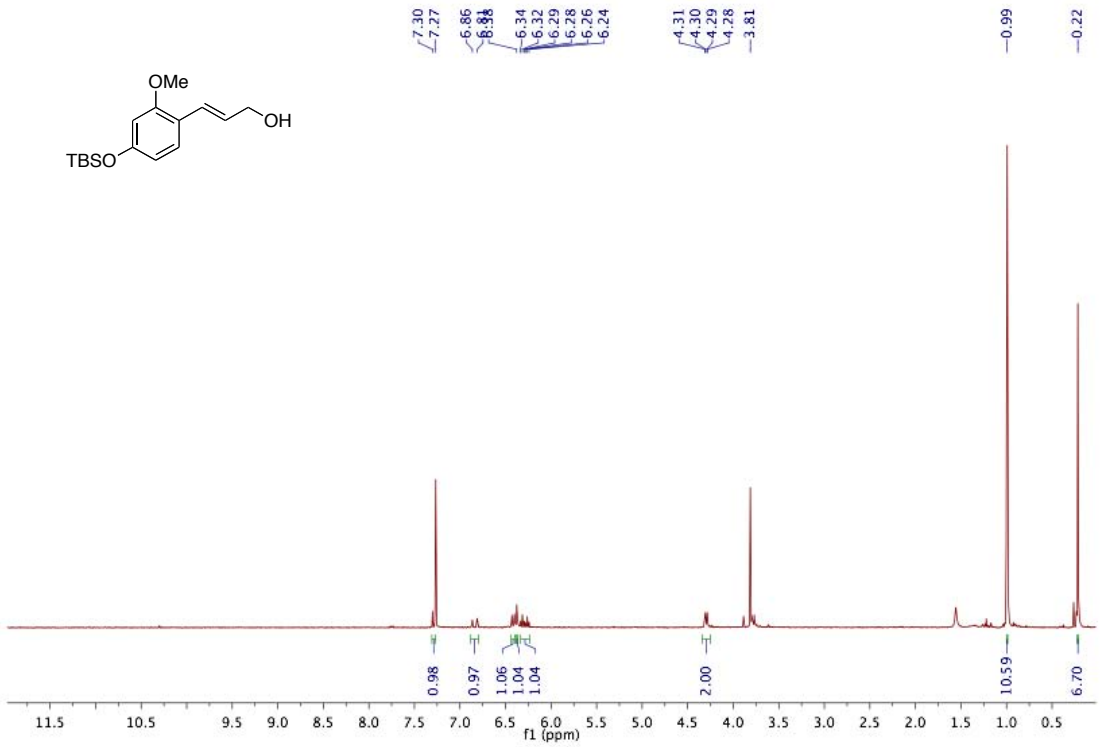

Br
OMe
OH

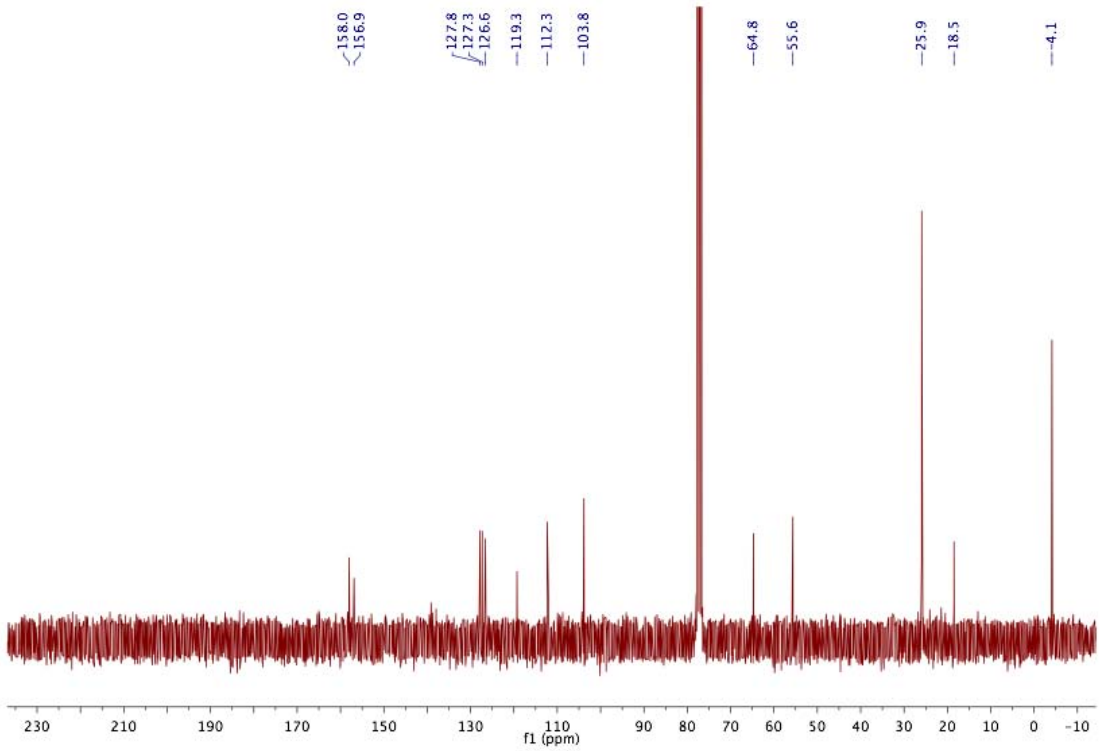
7.01
7.00
6.97
6.96
6.81
6.81
6.78
6.78
5.55
3.88
1.95
1.00
0.94
2.98
f1 (ppm)

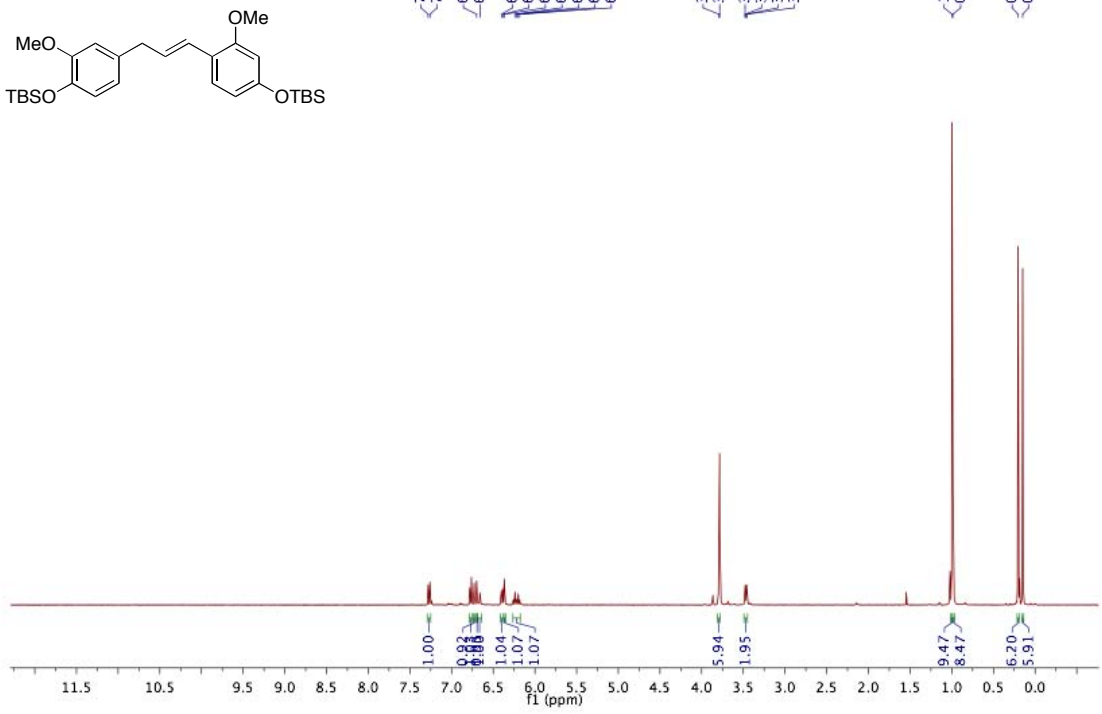

147.4
145.1
124.4
115.9
114.4
111.8
56.4
f1 (ppm)

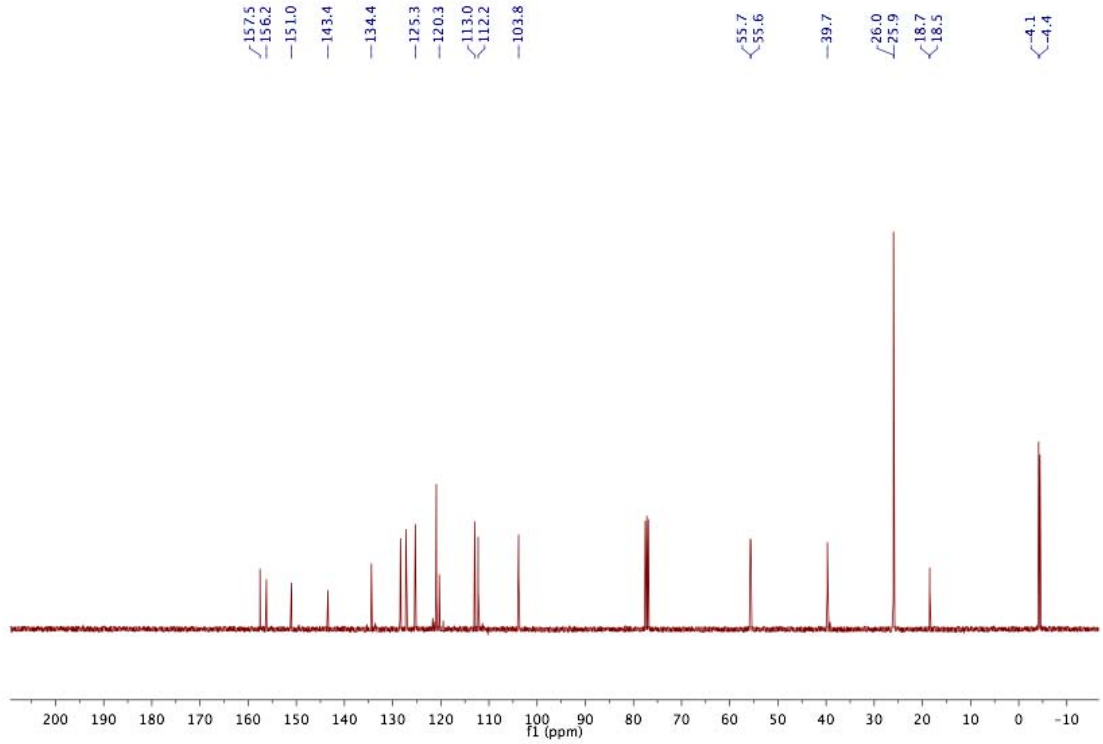

Br
OMe
OTBS
6.96
6.95
6.95
6.94
6.92
6.91
6.73
6.70
3.79
0.98
0.14
2.07
1.00
3.00
9.18
6.08
f1 (ppm)

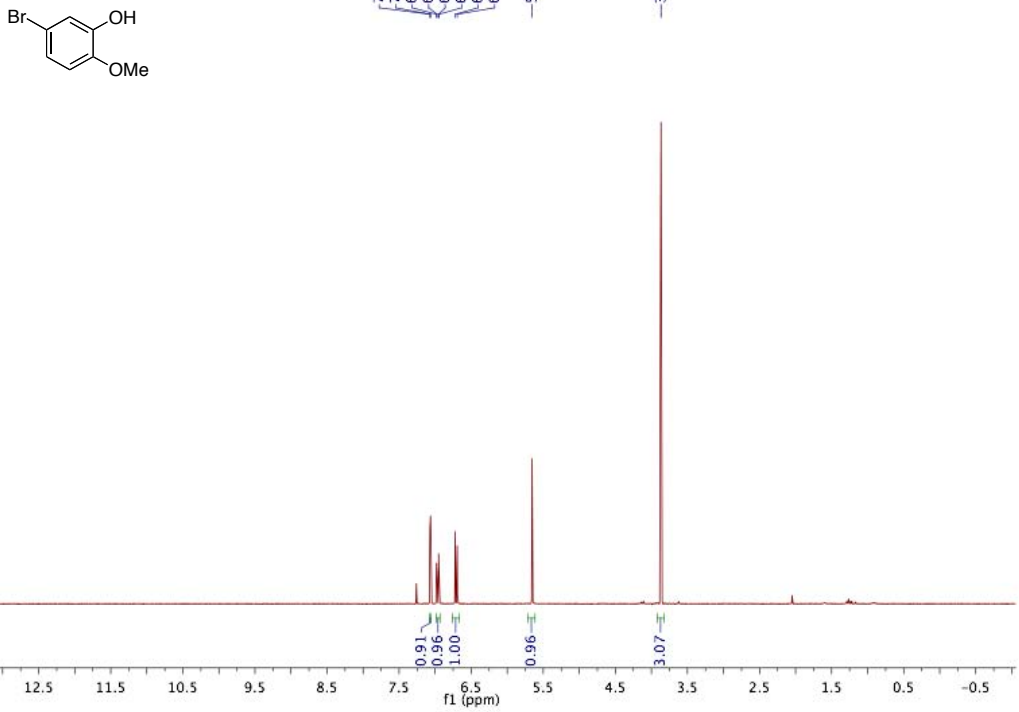

152.0
144.6
123.9
122.3
115.7
113.6
55.9
25.9
18.7
4.5
f1 (ppm)

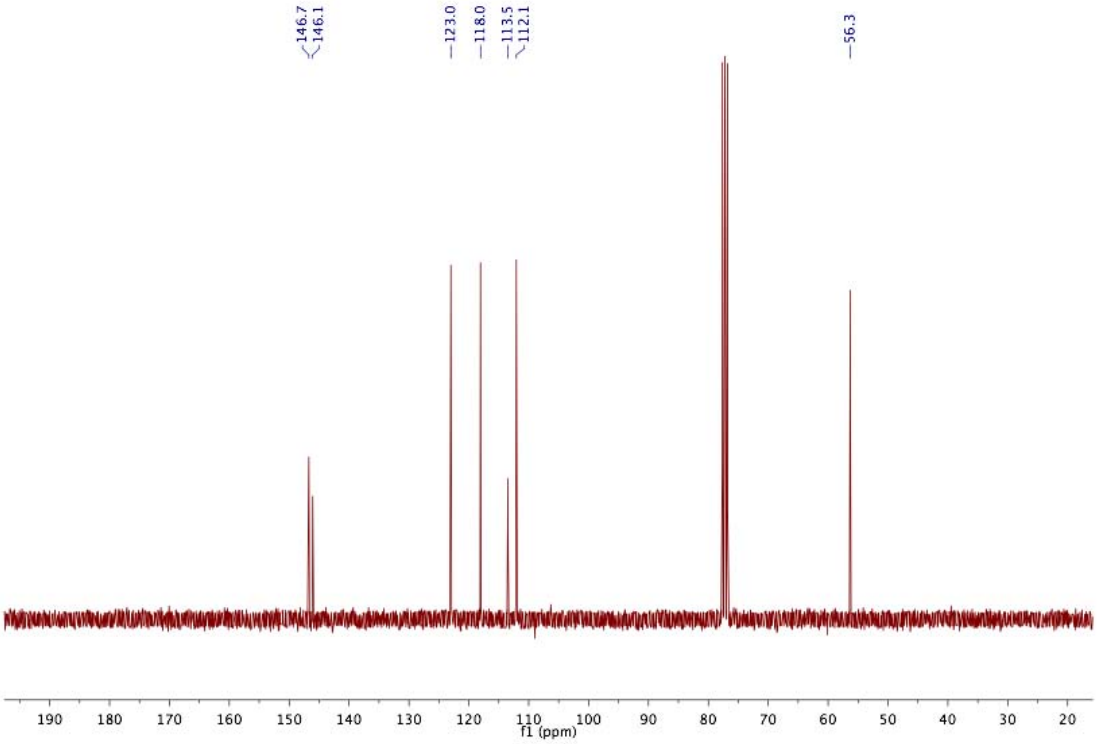

OMe
OH
TBSO
7.30
7.27
6.86
6.34
6.32
6.29
6.28
6.26
6.24
4.31
4.30
4.29
4.28
3.81
0.99
0.22
0.98
0.97
1.06
1.04
1.04
2.00
10.59
6.70
f1 (ppm)

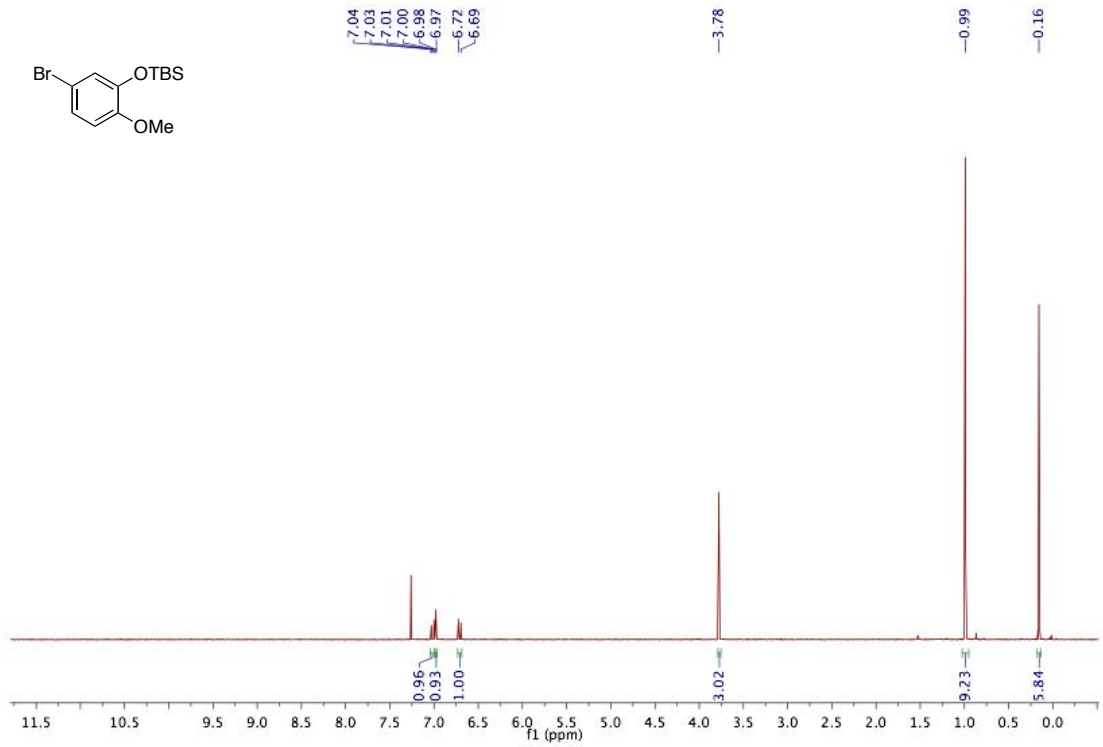

158.0
156.9
127.8
127.3
126.6
119.3
112.3
103.8
64.8
55.6
25.9
18.5
-4.1
f1 (ppm)

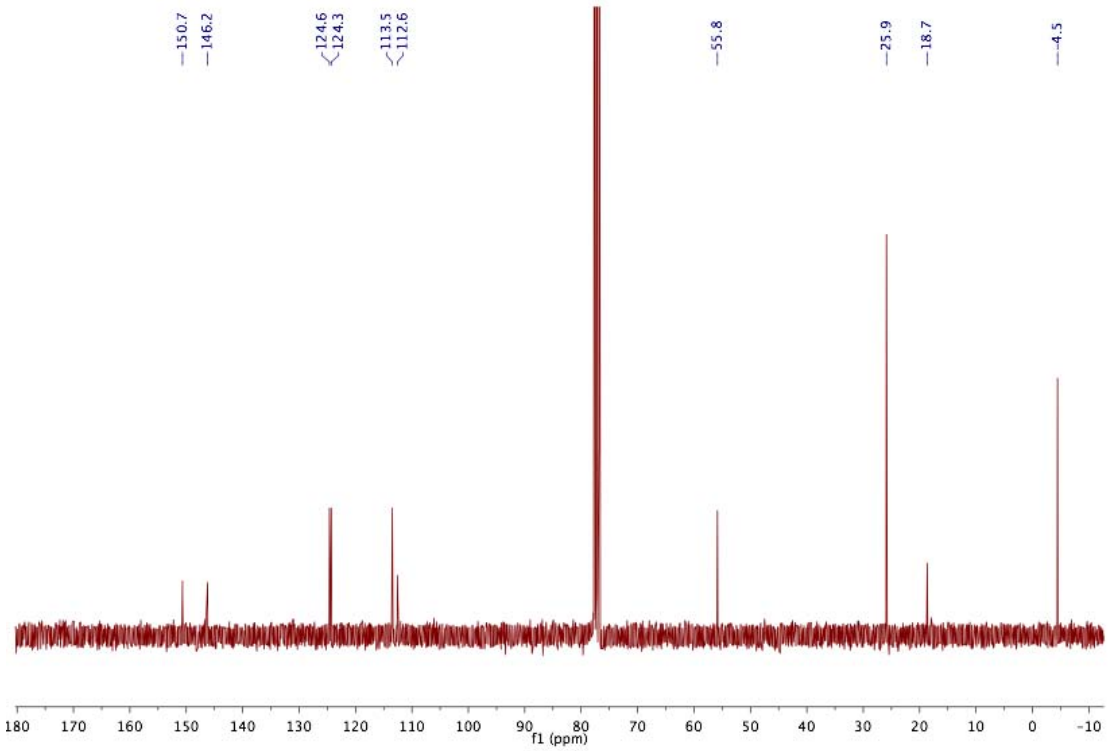

MeO
OMe
TBSO
OTBS
7.28
7.26
6.70
6.66
6.40
6.38
6.36
6.24
6.22
6.20
6.18
3.80
3.78
3.48
3.48
3.46
3.46
1.00
0.99
0.20
0.15
1.00
5.94
1.95
9.47
8.47
6.20
5.91
f1 (ppm)

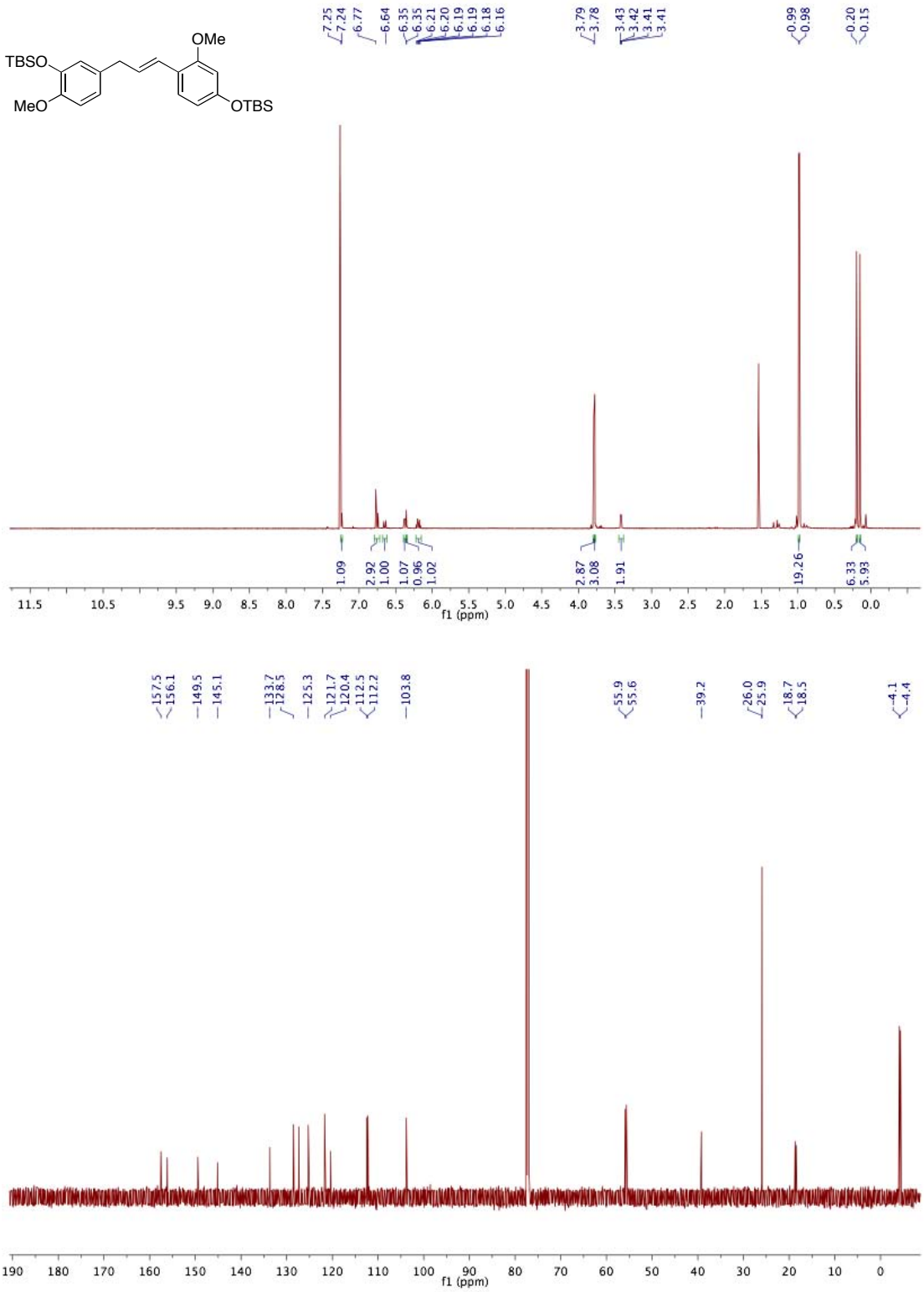

157.5
156.2
151.0
143.4
134.4
125.3
120.3
113.0
112.2
103.8
55.7
55.6
39.7
26.0
25.9
18.7
18.5
-4.1
-4.4
f1 (ppm)

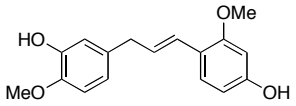

Br
OH
OMe
7.07
7.06
6.98
6.97
6.95
6.94
6.72
6.69
5.65
3.87
0.91
0.96
1.00
0.96
3.07
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)


146.7
146.1
123.0
118.0
113.5
112.1
56.3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

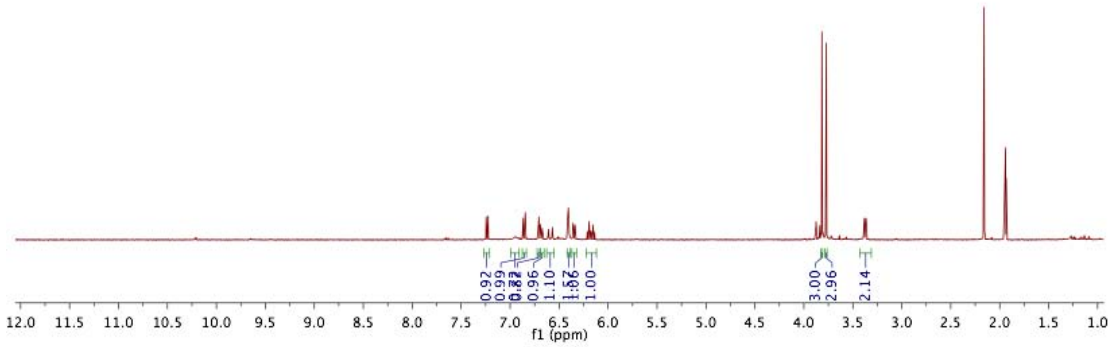

Br
OTBS
OMe
7.04
7.03
7.01
7.00
6.98
6.97
6.72
6.69
3.78
0.99
0.16
0.96
0.93
1.00
3.02
9.23
5.84
f1 (ppm)

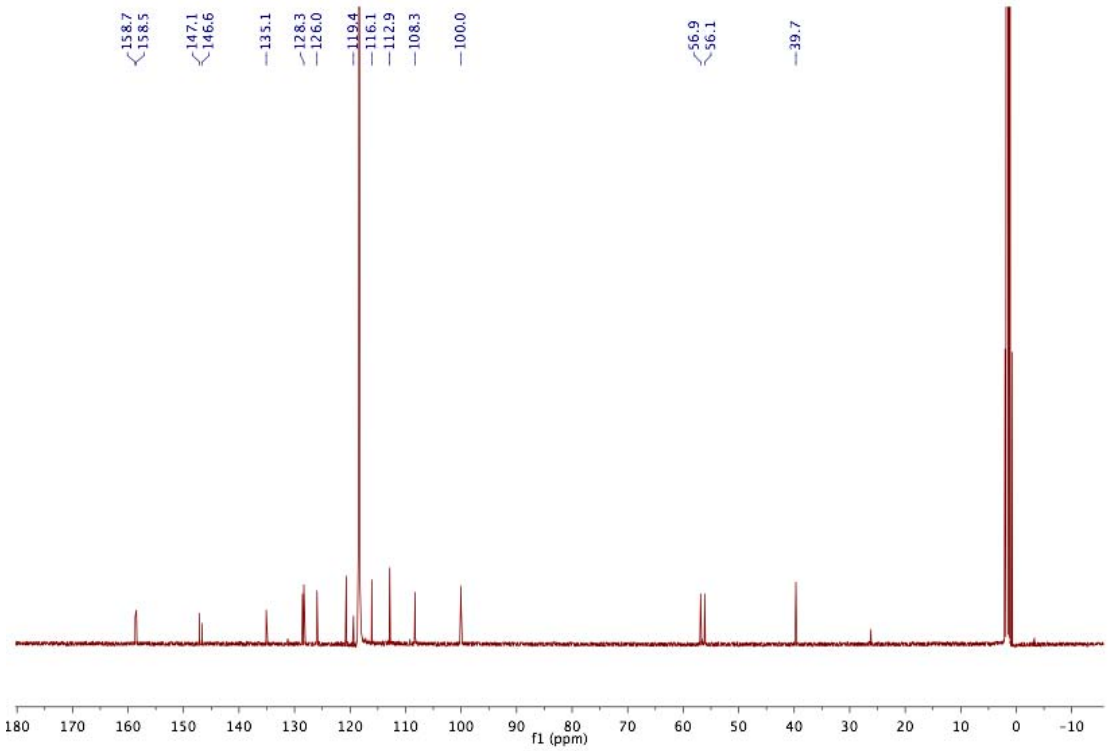

150.7
146.2
124.6
124.3
113.5
112.6
55.8
25.9
18.7
-4.5
f1 (ppm)

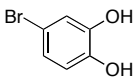

TBSO
OMe
MeO
OTBS
7.25
7.24
6.77
6.64
6.35
6.35
6.21
6.20
6.19
6.19
6.18
6.16
3.79
3.78
3.43
3.42
3.41
3.41
0.99
0.98
0.20
0.15
1.09
2.92
1.00
1.07
0.96
1.02
2.87
3.08
1.91
19.26
6.33
5.93
f1 (ppm)
157.5
156.1
149.5
145.1
133.7
128.5
125.3
121.7
120.4
112.5
112.2
103.8
55.9
55.6
39.2
26.0
25.9
18.7
18.5
-4.1
-4.4
f1 (ppm)


OMe
HO
MeO
OH

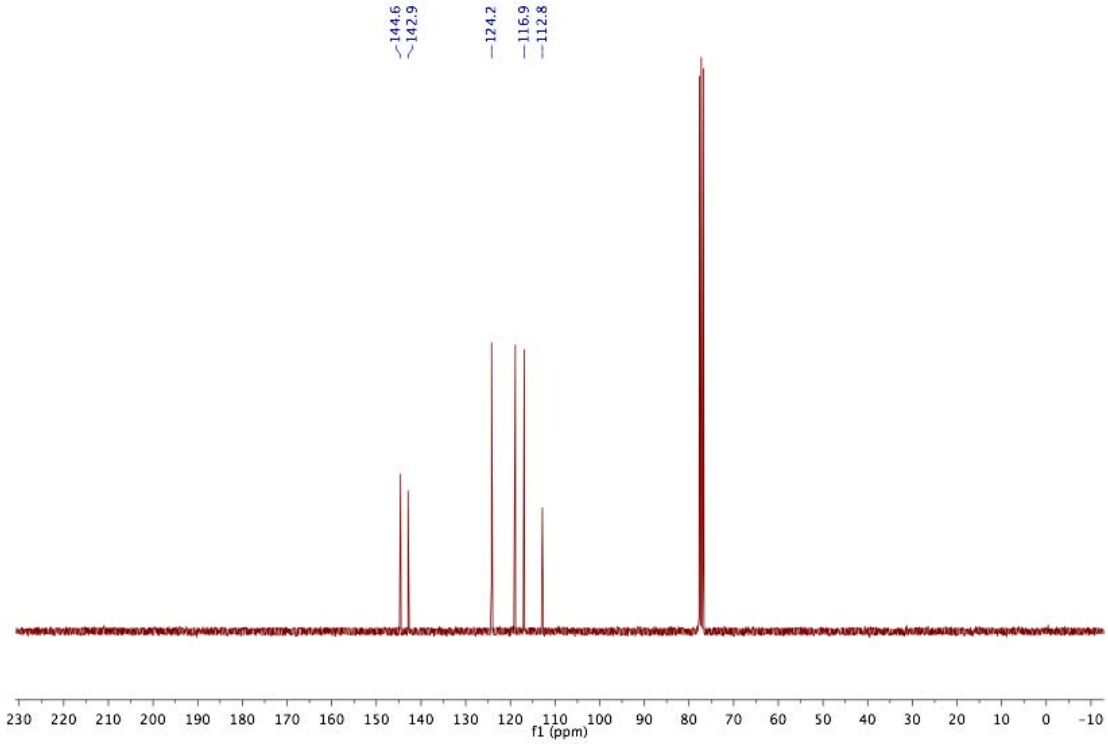

7.25
7.22
6.85
6.41
6.36
6.35
6.34
6.33
6.21
6.19
6.18
6.17
6.15
6.14
3.82
3.77
3.39
3.38
3.37
3.36

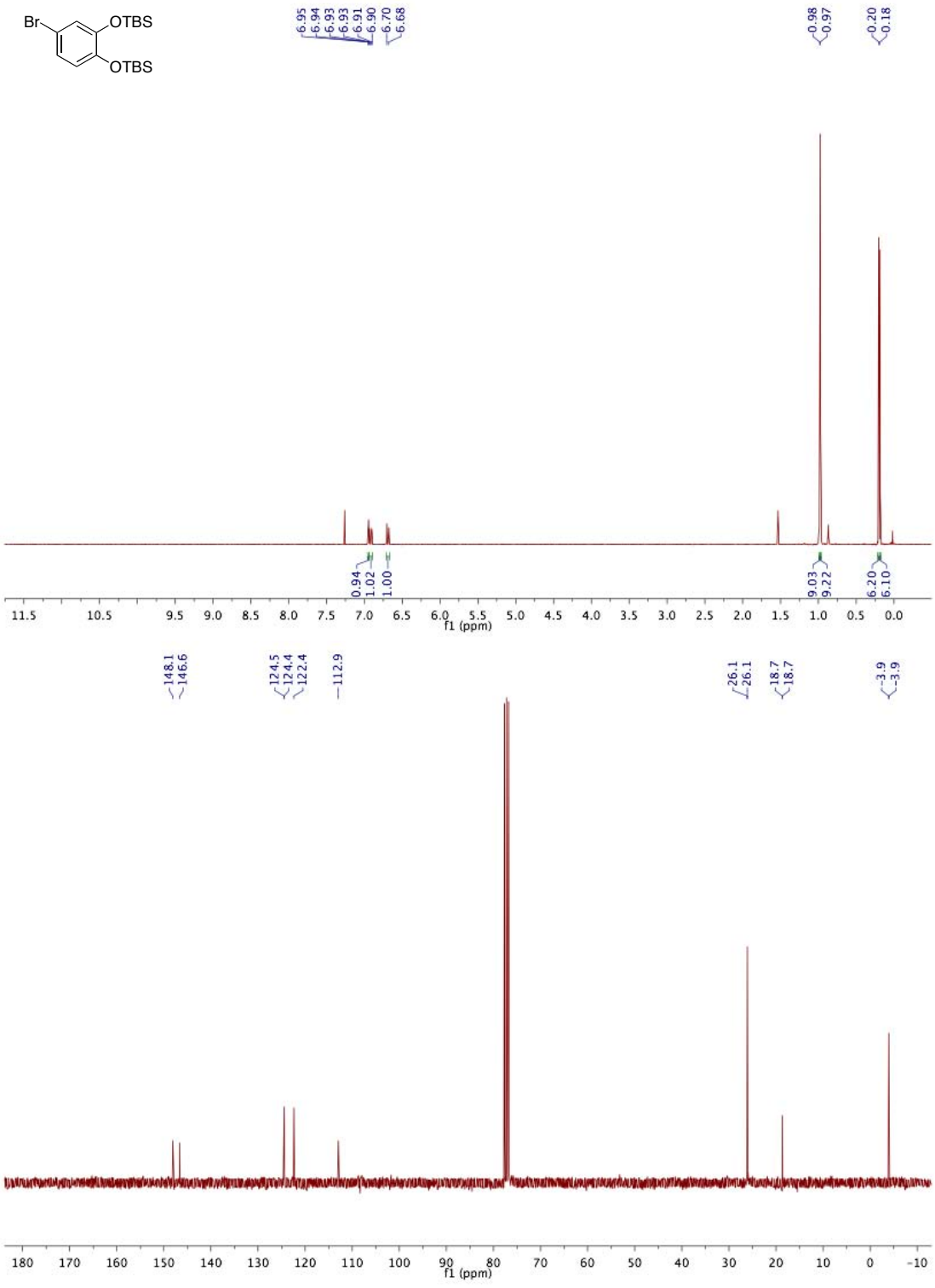

0.92
0.99
0.96
1.10
1.00
3.00
2.96
2.14
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

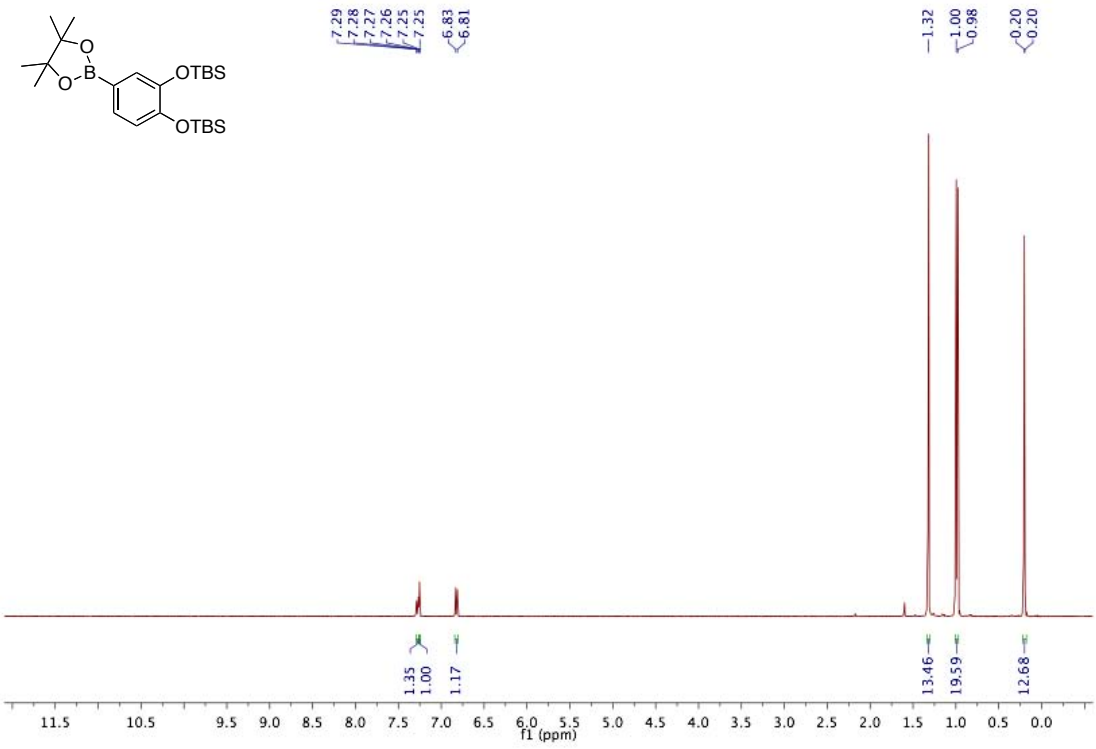

158.7
158.5
147.1
146.6
135.1
128.3
126.0
119.4
116.1
112.9
108.3
100.0
56.9
56.1
39.7
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

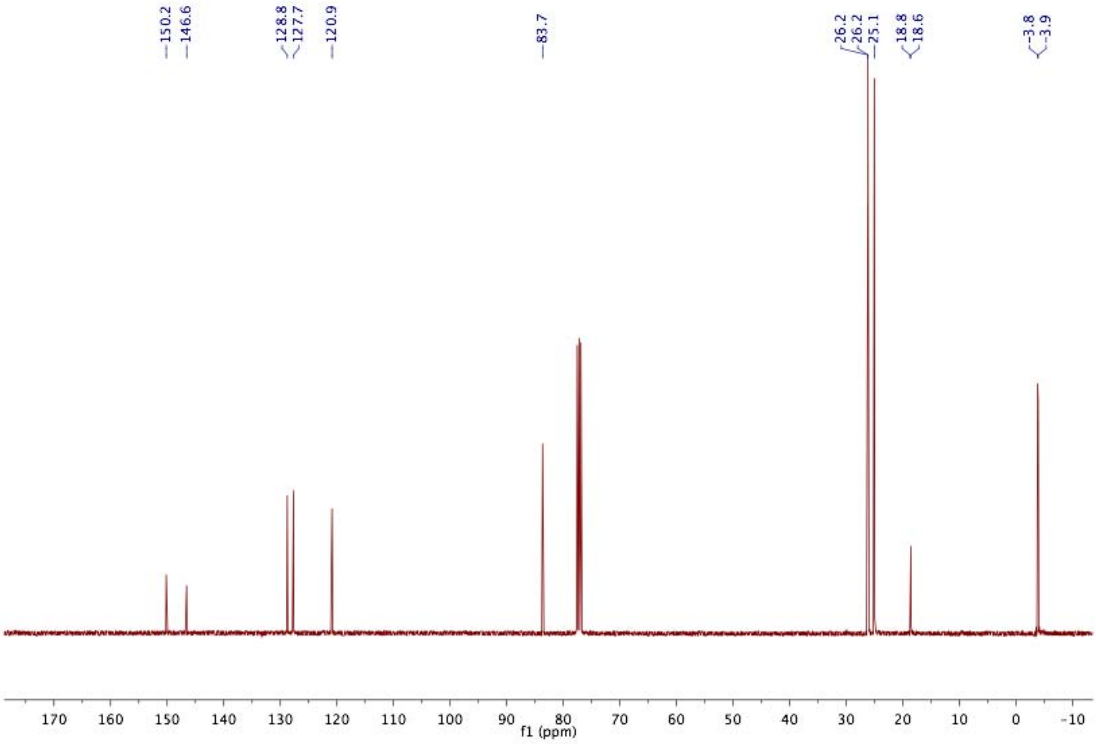

Br
OH
OH

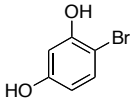
7.03
7.02
6.95
6.94
6.92
6.91
6.76
6.73
5.45
5.32
1.00
1.02
1.04
1.87
f1 (ppm)


144.6
142.9
124.2
116.9
112.8
f1 (ppm)

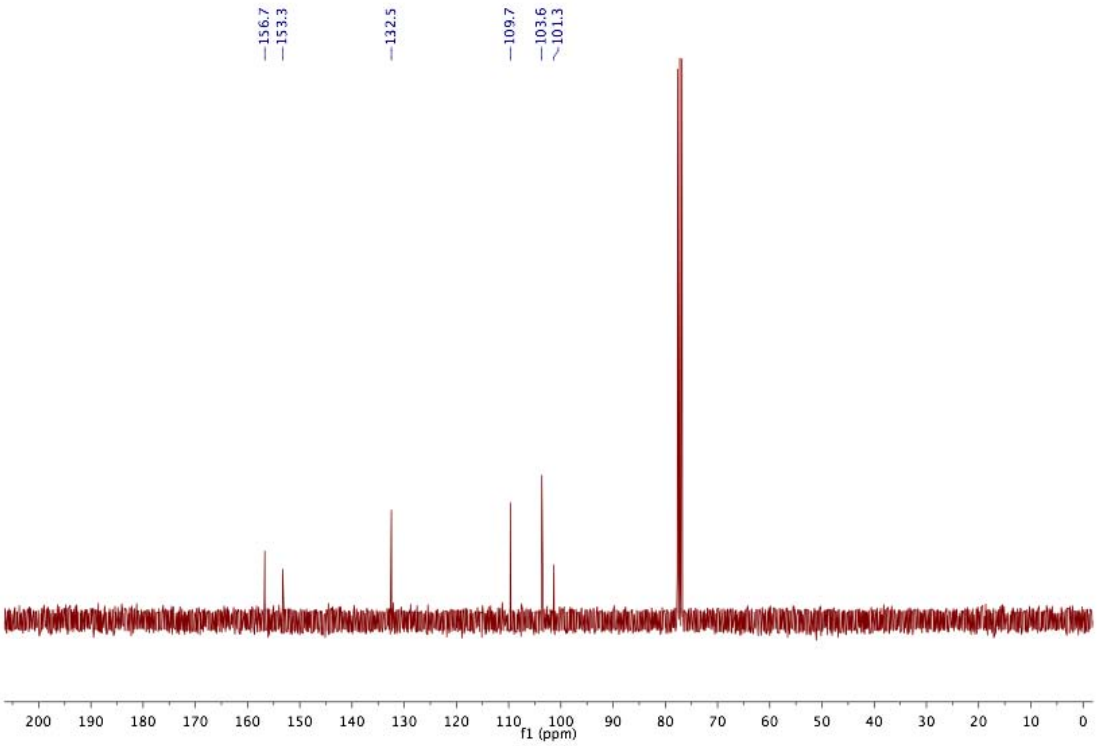

Br
OTBS
OTBS
6.95
6.94
6.93
6.93
6.91
6.90
6.70
6.68
0.98
0.97
0.20
0.18
0.94
1.02
1.00
9.03
9.22
6.20
6.10
f1 (ppm)
148.1
146.6
124.5
124.4
122.4
112.9
26.1
26.1
18.7
18.7
-3.9
-3.9
f1 (ppm)

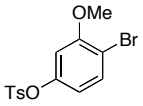

OTBS
OTBS
7.29
7.28
7.27
7.26
7.25
7.25
6.83
6.81
1.32
1.00
0.98
0.20
0.20
1.35
1.00
1.17
13.46
19.59
12.68
f1 (ppm)


150.2
146.6
128.8
127.7
120.9
83.7
26.2
26.2
25.1
18.8
18.6
-3.8
-3.9
f1 (ppm)

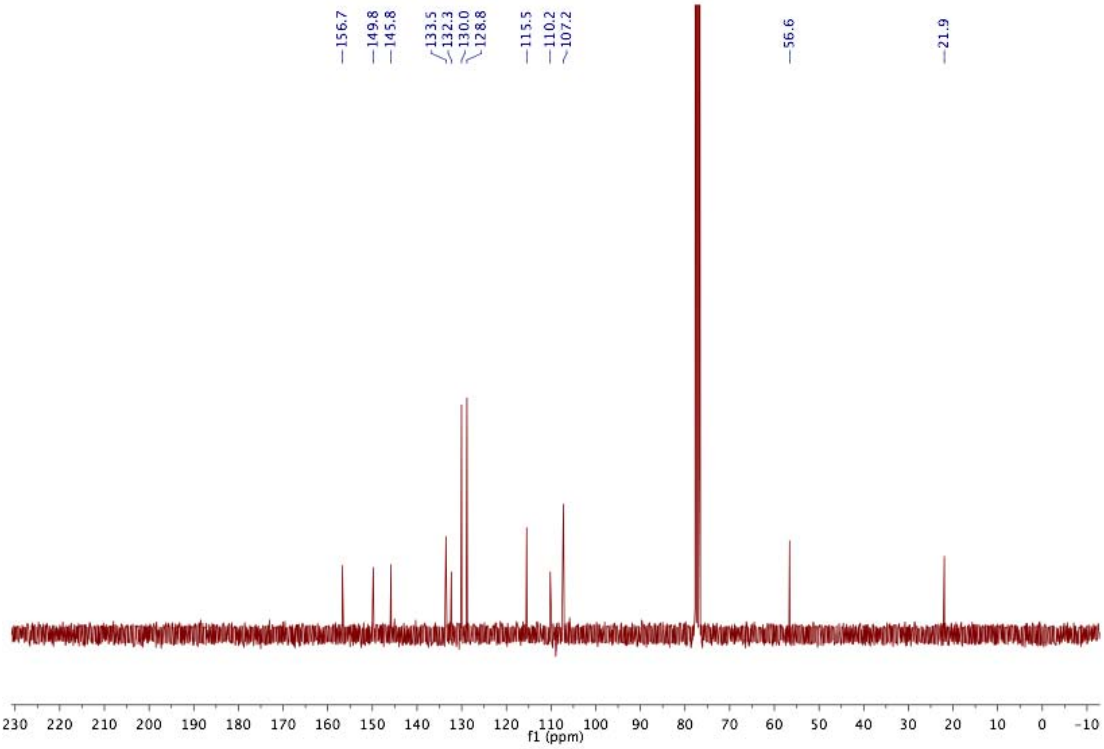

OH
Br
HO

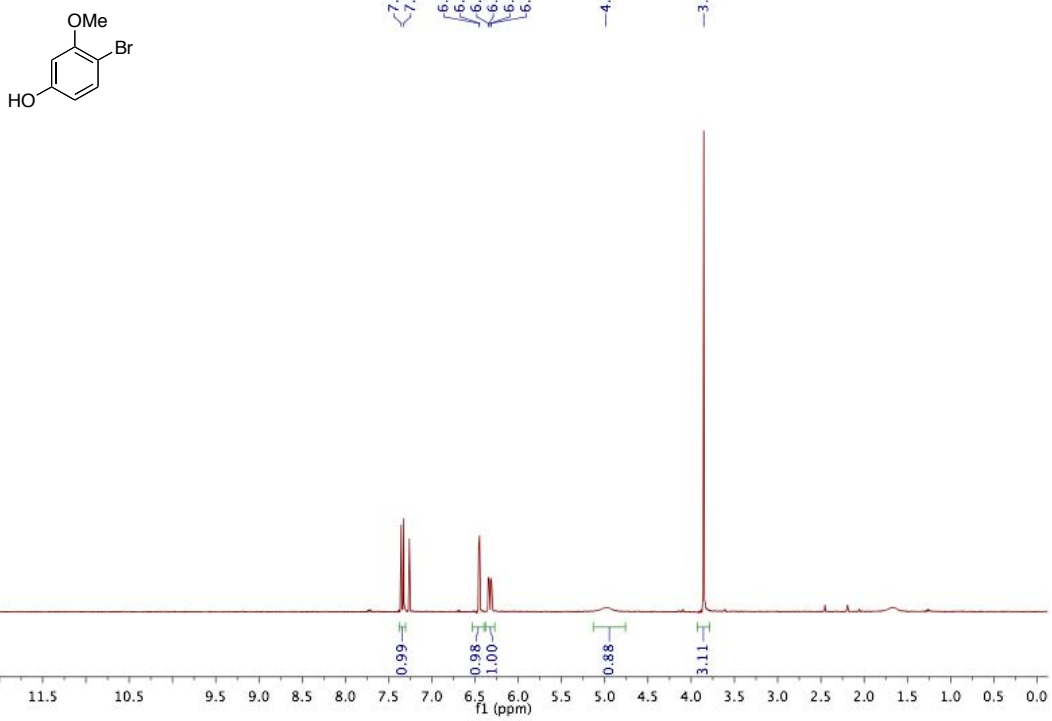
7.29
7.27
6.55
6.54
6.36
6.34
6.33
5.48
4.90
0.96
1.00
1.03
0.96
0.97
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

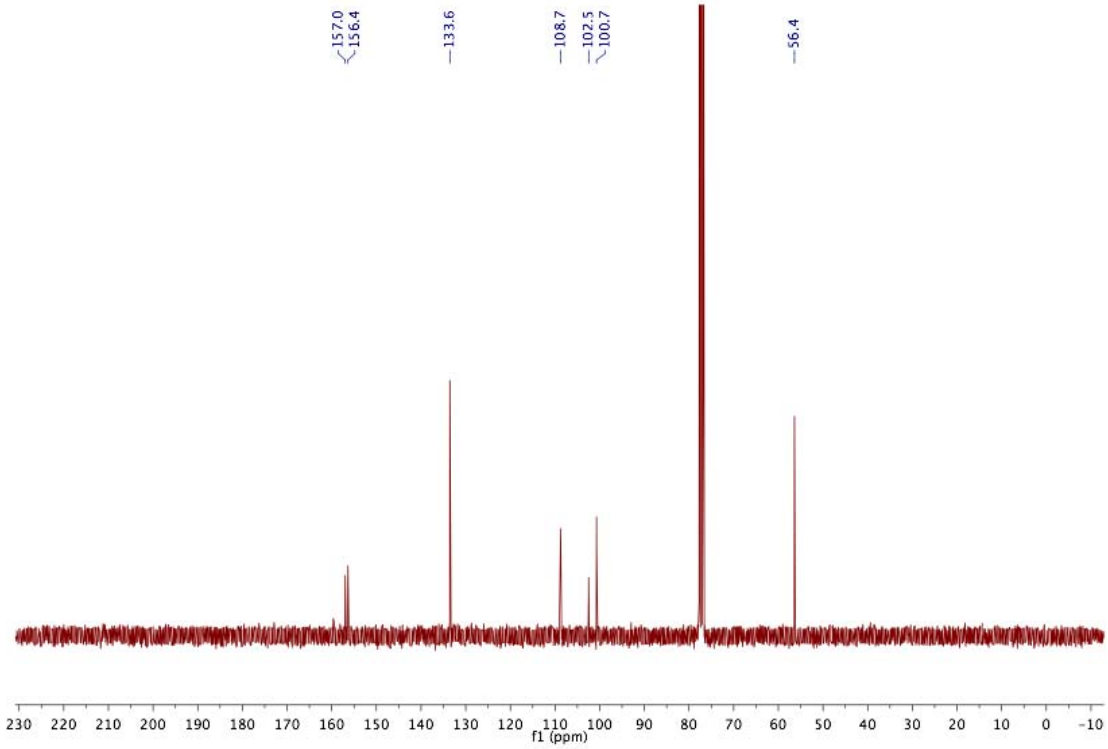

156.7
153.3
132.5
109.7
103.6
101.3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

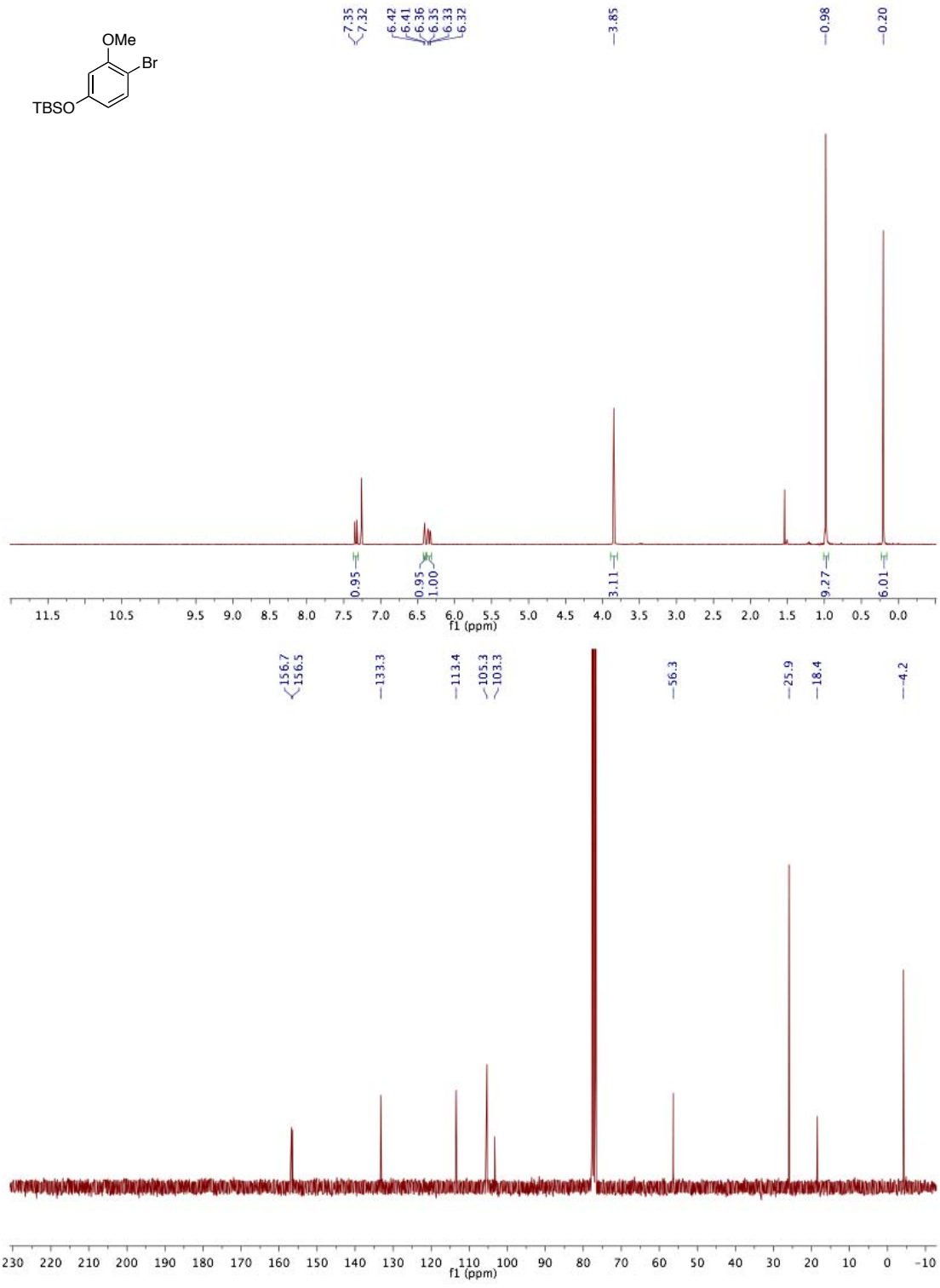

OMe
Br
TsO

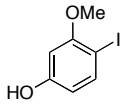
7.73
7.70
7.31
6.60
6.59
6.42
6.42
6.40
6.39
3.78
2.46
1.91
0.99
2.13
0.99
1.00
3.17
3.10
f1 (ppm)


156.7
149.8
145.8
133.5
132.3
130.0
128.8
115.5
110.2
107.2
56.6
21.9
f1 (ppm)

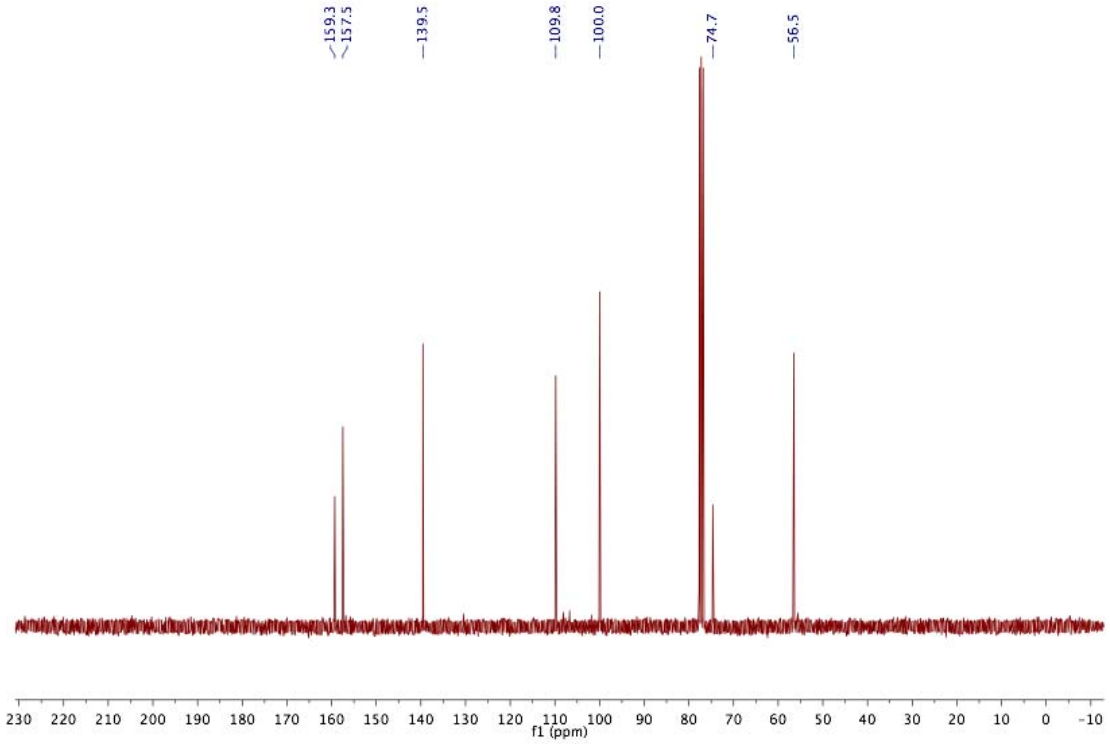

OMe
Br
HO
7.35
7.33
6.46
6.45
6.35
6.34
6.32
6.31
4.99
3.85
0.99
0.98
1.00
0.88
3.11
f1 (ppm)

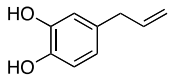

157.0
156.4
133.6
108.7
102.5
100.7
56.4
f1 (ppm)


OMe
Br
TBSO
7.35
7.32
6.42
6.41
6.36
6.35
6.33
6.32
3.85
0.98
0.20
0.95
0.95
1.00
3.11
9.27
6.01
f1 (ppm)
156.7
156.5
133.3
113.4
105.3
103.3
56.3
25.9
18.4
-4.2
f1 (ppm)

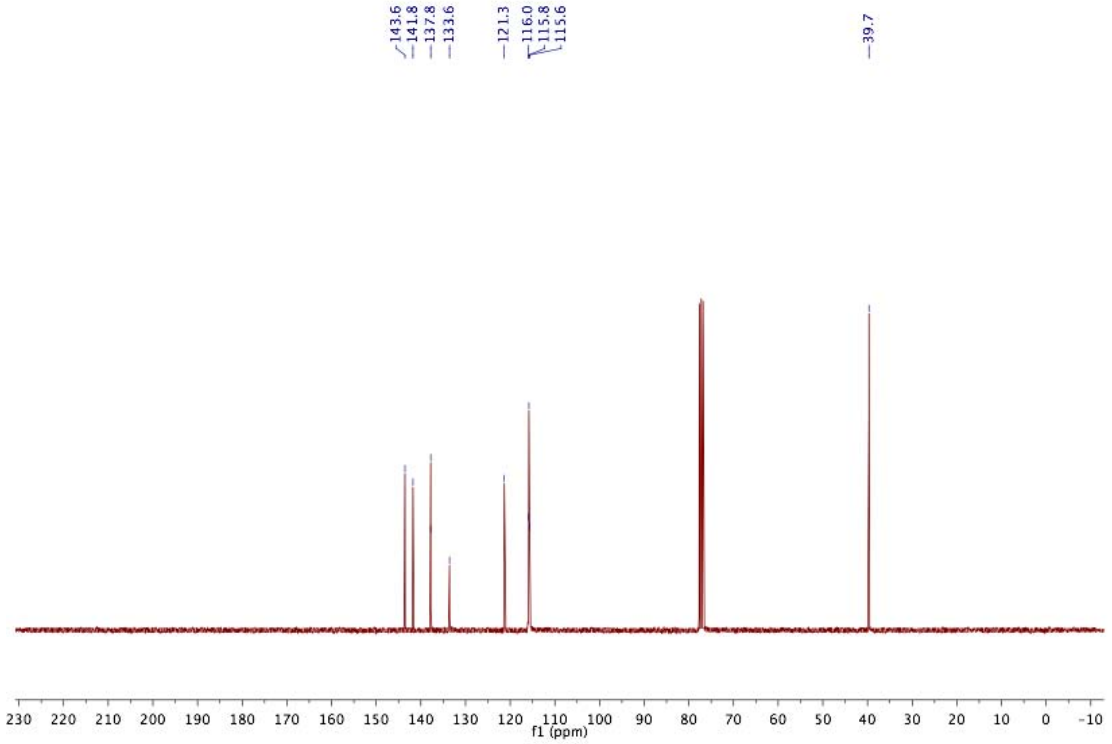

OMe
I
HO

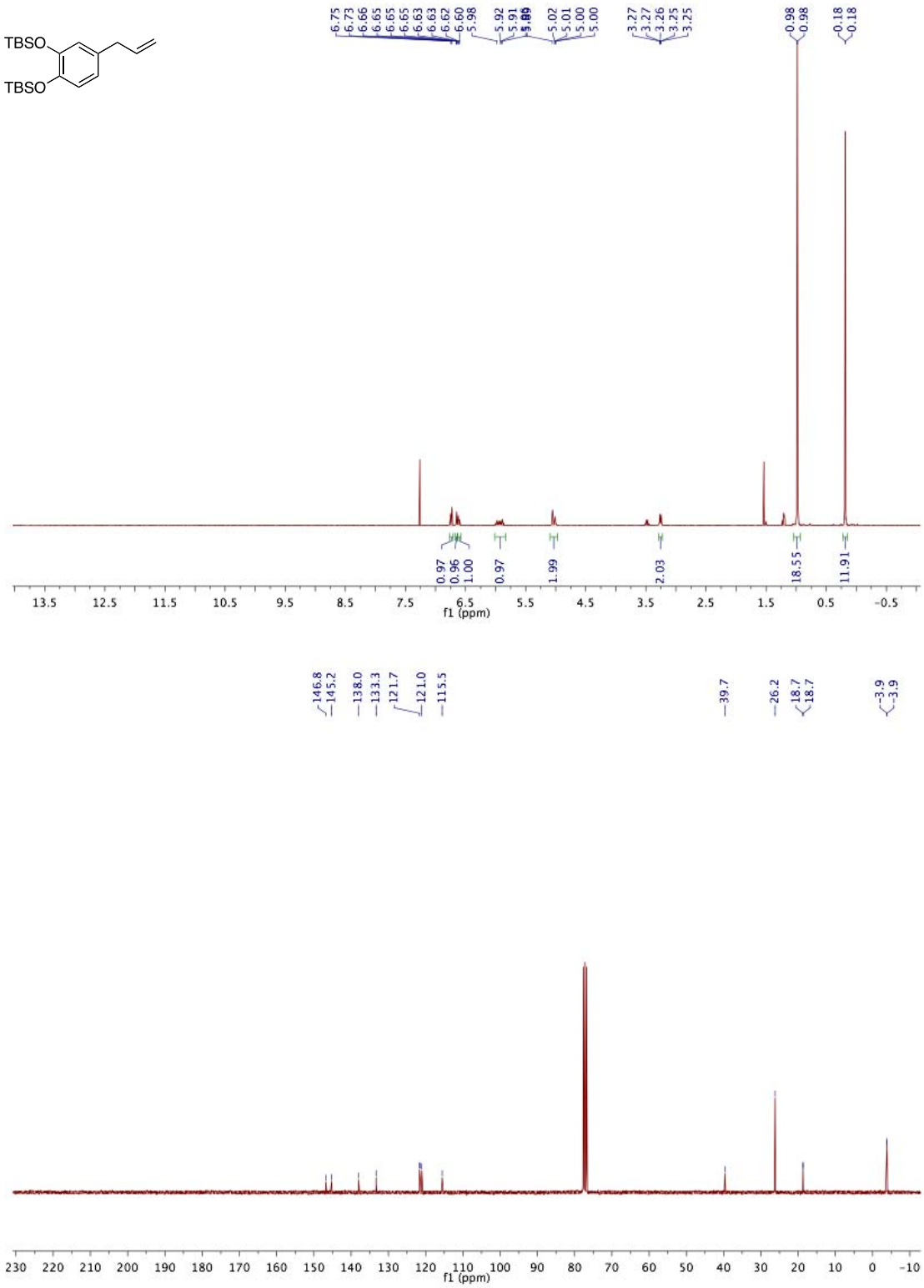
7.56
7.53
6.40
6.39
6.27
6.27
6.25
6.24
3.83
0.96
1.06
1.00
0.78
3.09
f1 (ppm)

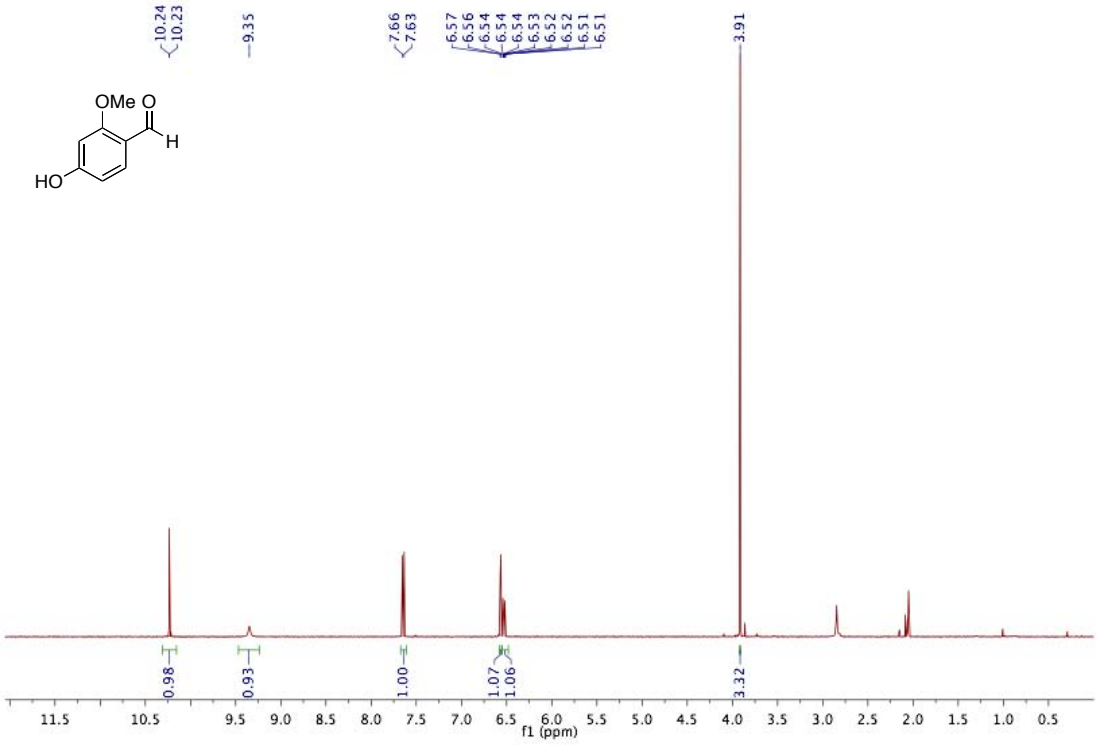

159.3
157.5
139.5
109.8
100.0
74.7
56.5
f1 (ppm)

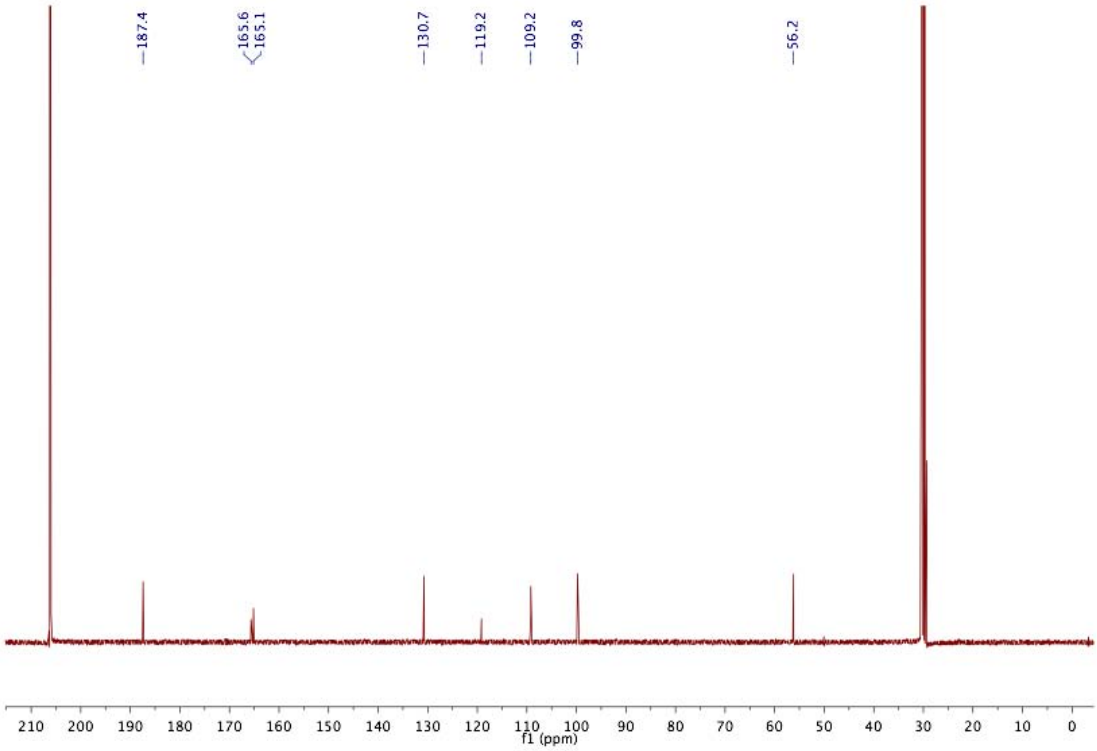

HO
HO

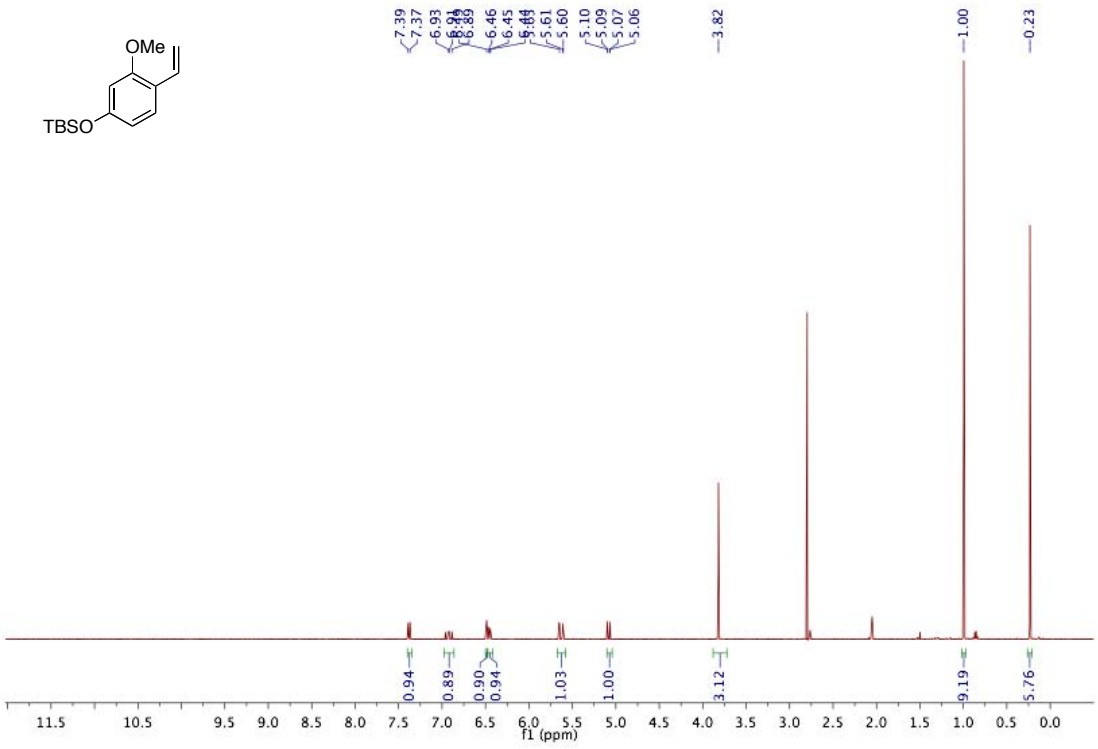
6.81
6.79
6.72
6.72
6.65
6.65
6.63
5.91
5.88
5.86
5.41
5.09
5.07
5.07
5.04
5.03
3.29
3.26
1.07
1.04
1.05
1.07
2.25
1.14
1.00
2.24
f1 (ppm)

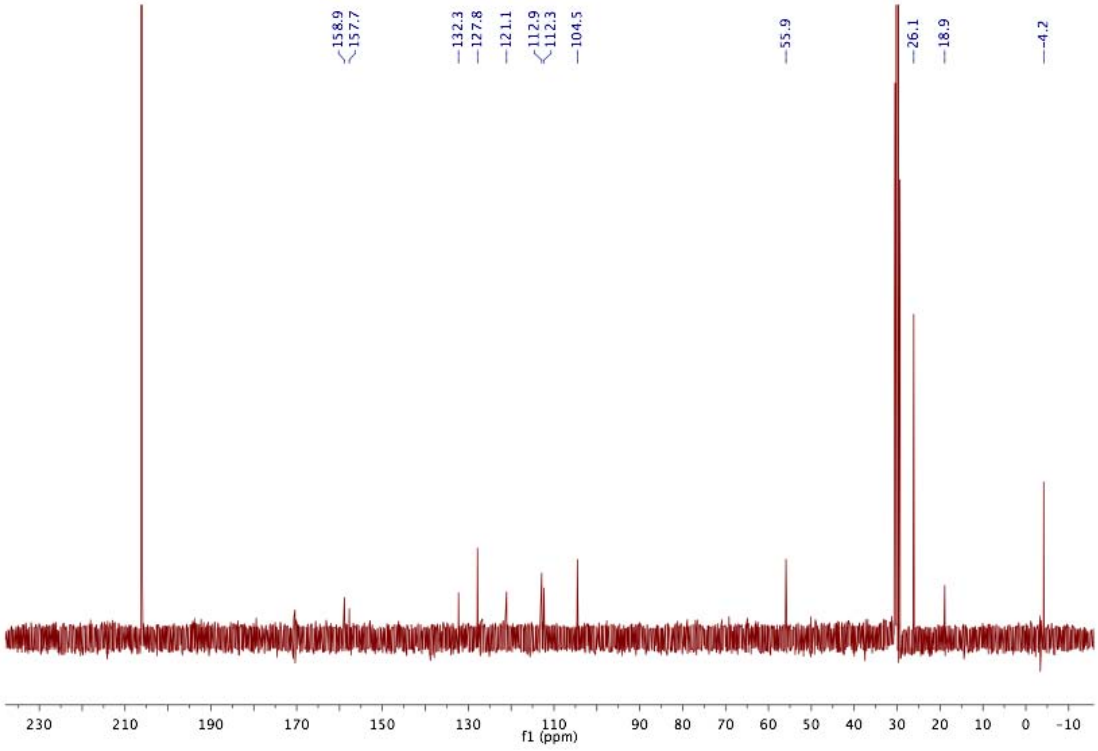

143.6
141.8
137.8
133.6
121.3
116.0
115.8
115.6
39.7
f1 (ppm)

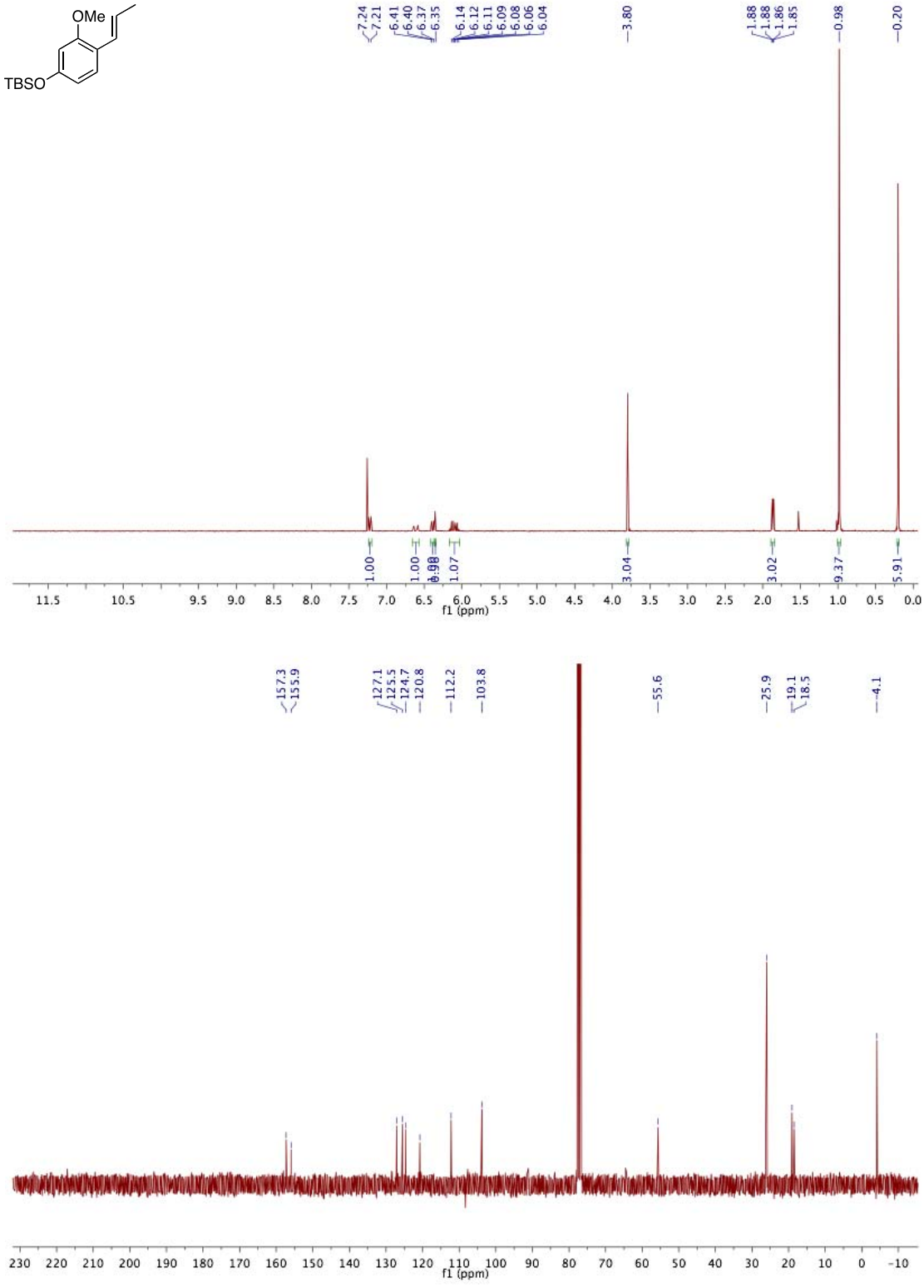

TBSO
TBSO
6.75
6.73
6.66
6.65
6.65
6.65
6.63
6.62
6.60
5.98
5.92
5.91
5.02
5.01
5.00
5.00
3.27
3.27
3.26
3.25
3.25
0.98
0.98
0.18
0.18
0.97
0.96
1.00
0.97
1.99
2.03
18.55
11.91
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)
146.8
145.2
138.0
133.3
121.7
121.0
115.5
39.7
26.2
18.7
18.7
-3.9
-3.9
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

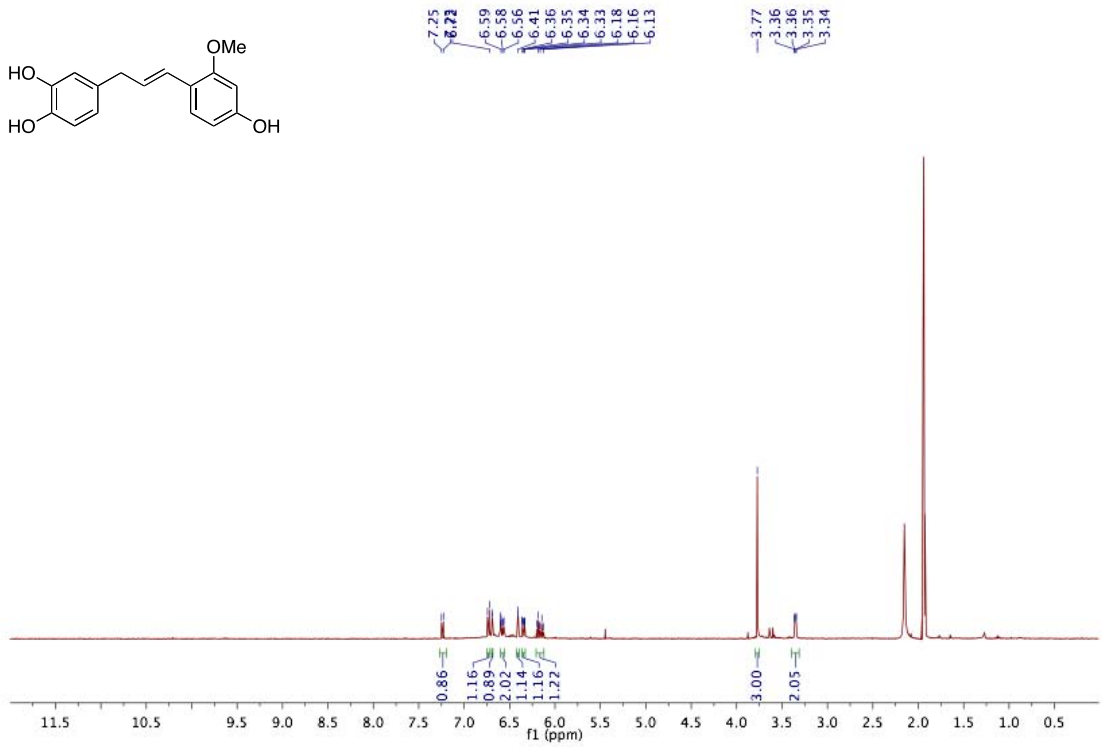

10.24
10.23
9.35
7.66
7.63
6.57
6.56
6.54
6.54
6.54
6.53
6.52
6.52
6.51
6.51
3.91
OMe O
H
HO
0.98
0.93
1.00
1.07
1.06
3.32
f1 (ppm)

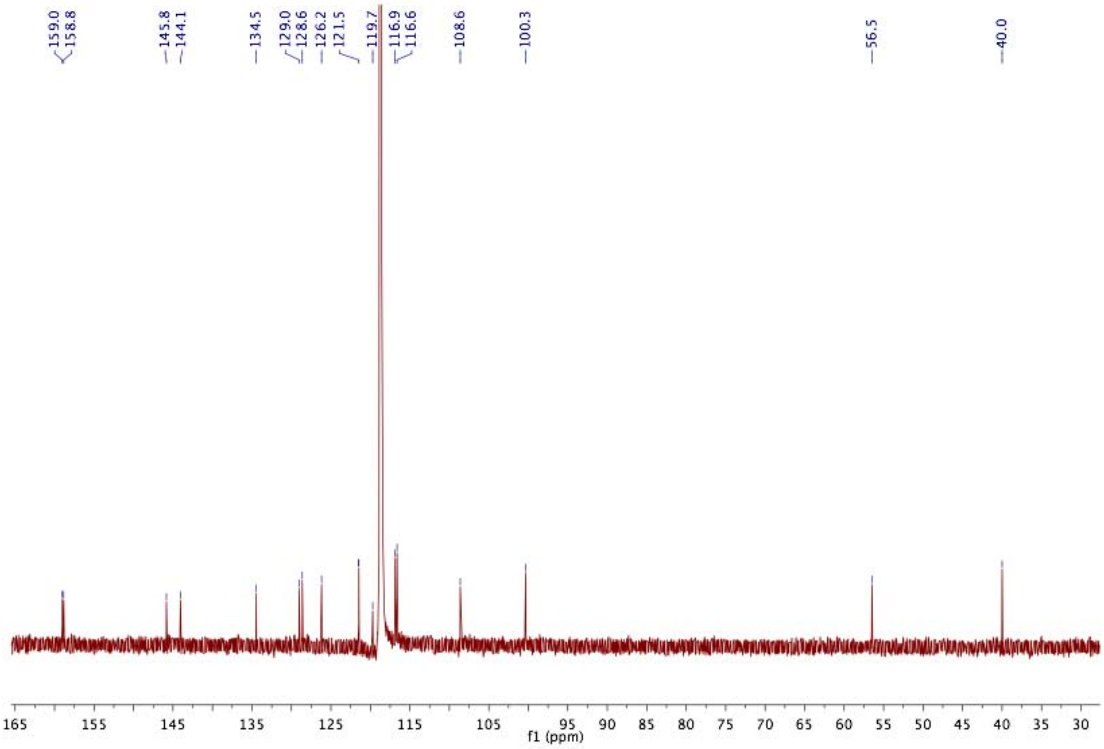

187.4
165.6
165.1
130.7
119.2
109.2
99.8
56.2
f1 (ppm)

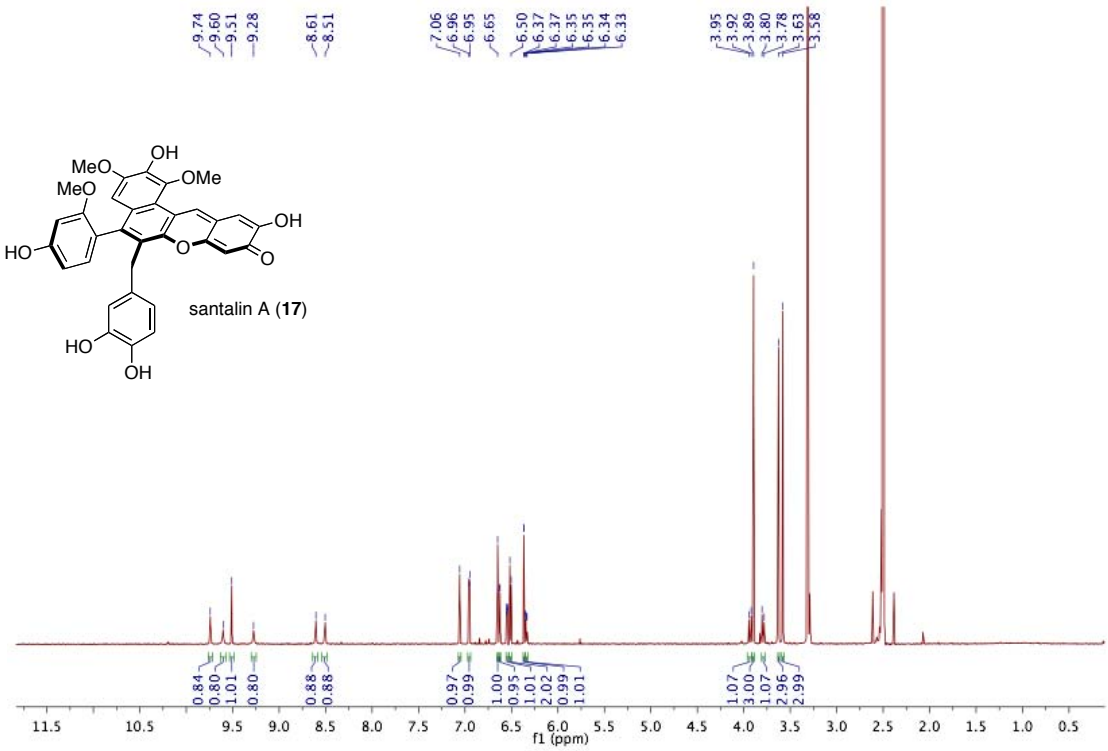

OMe
TBSO
7.39
7.37
6.93
6.46
6.45
5.61
5.60
5.10
5.09
5.07
5.06
3.82
1.00
0.23
0.94
0.89
0.90
0.94
1.03
1.00
3.12
9.19
5.76
f1 (ppm)


158.9
157.7
132.3
127.8
121.1
112.9
112.3
104.5
55.9
26.1
18.9
4.2
f1 (ppm)

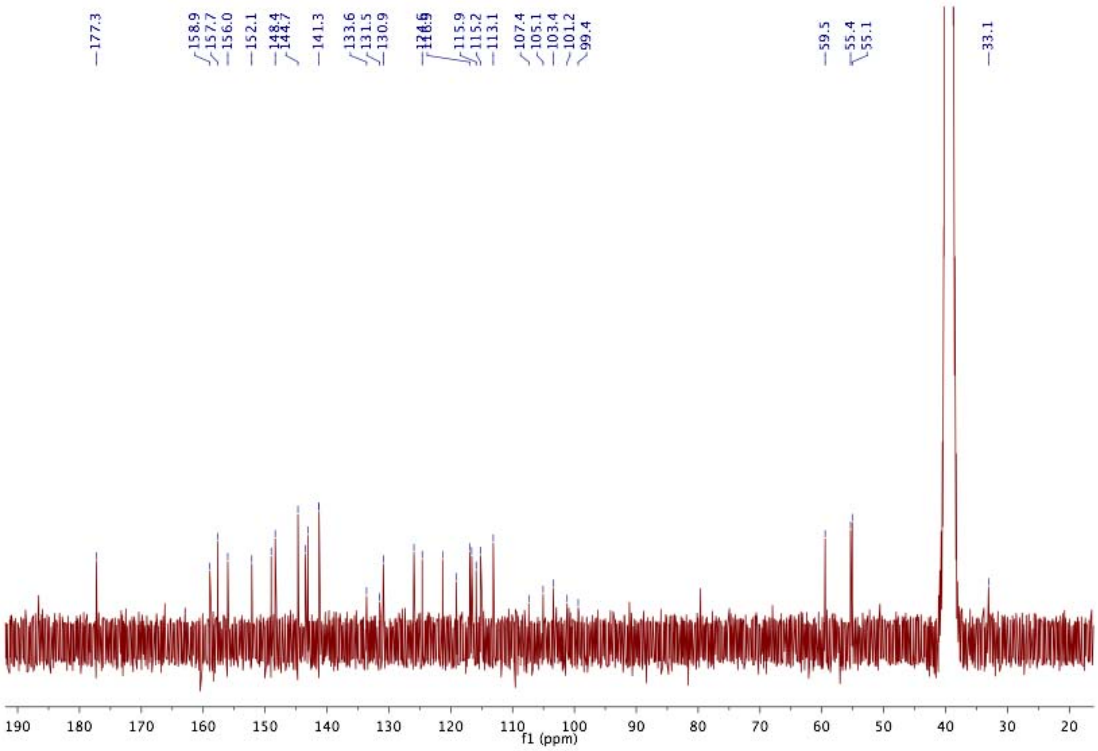

OMe
TBSO
7.24
7.21
6.41
6.40
6.37
6.35
6.14
6.12
6.11
6.09
6.08
6.06
6.04
3.80
1.88
1.88
1.86
1.85
0.98
0.20
1.00
1.00
1.07
3.04
3.02
9.37
5.91
f1 (ppm)
157.3
155.9
127.1
125.5
124.7
120.8
112.2
103.8
55.6
25.9
19.1
18.5
-4.1
f1 (ppm)

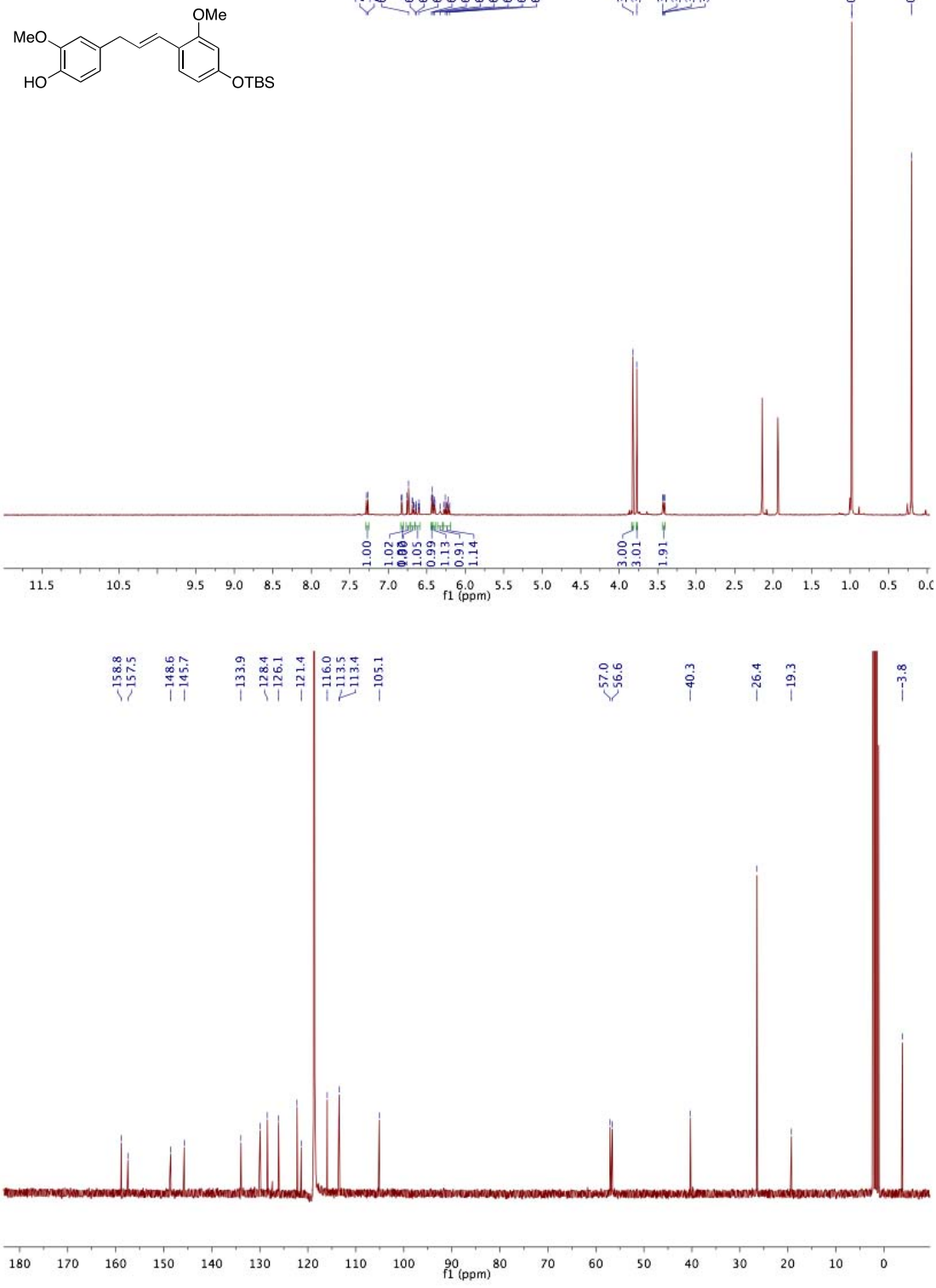

HO
HO
OMe
OH
7.25
6.59
6.58
6.56
6.41
6.36
6.35
6.34
6.33
6.18
6.16
6.13
3.77
3.36
3.36
3.35
3.34
0.86
1.16
0.89
2.02
1.14
1.16
1.22
3.00
2.05
f1 (ppm)

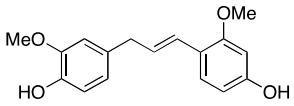

159.0
158.8
145.8
144.1
134.5
129.0
128.6
126.2
121.5
119.7
116.9
116.6
108.6
100.3
56.5
40.0
f1 (ppm)



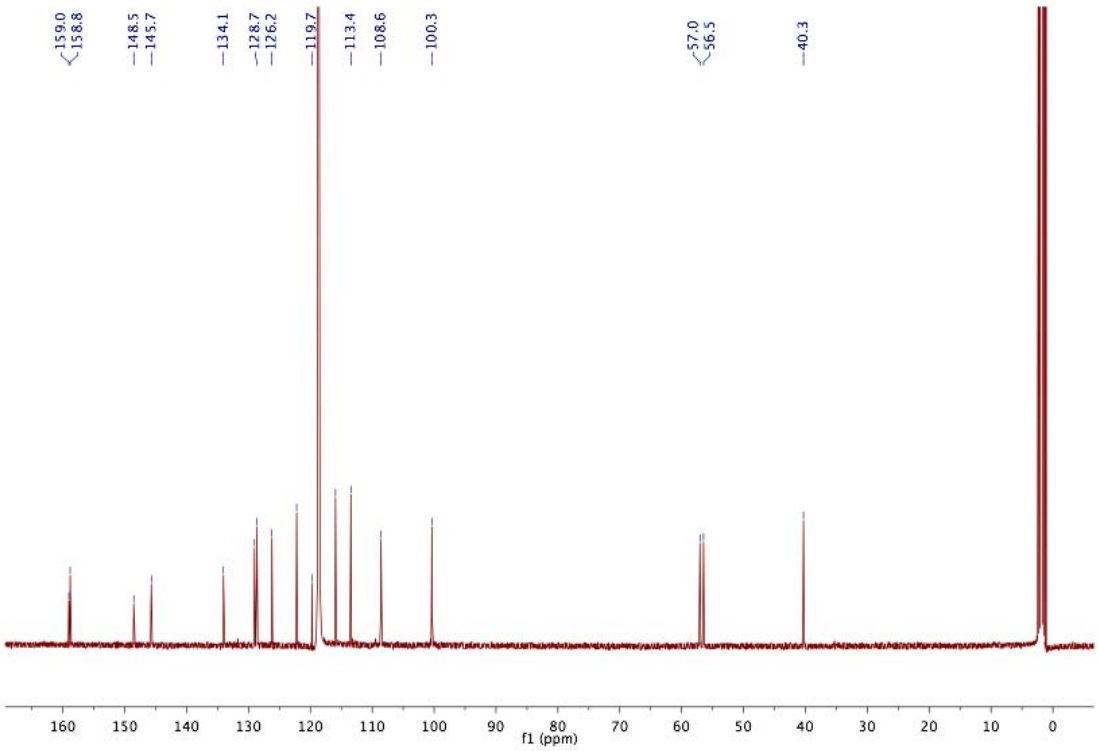
santalin A (**17**)

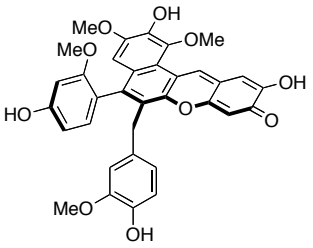



MeO
HO
OMe
OTBS
f1 (ppm)
f1 (ppm)

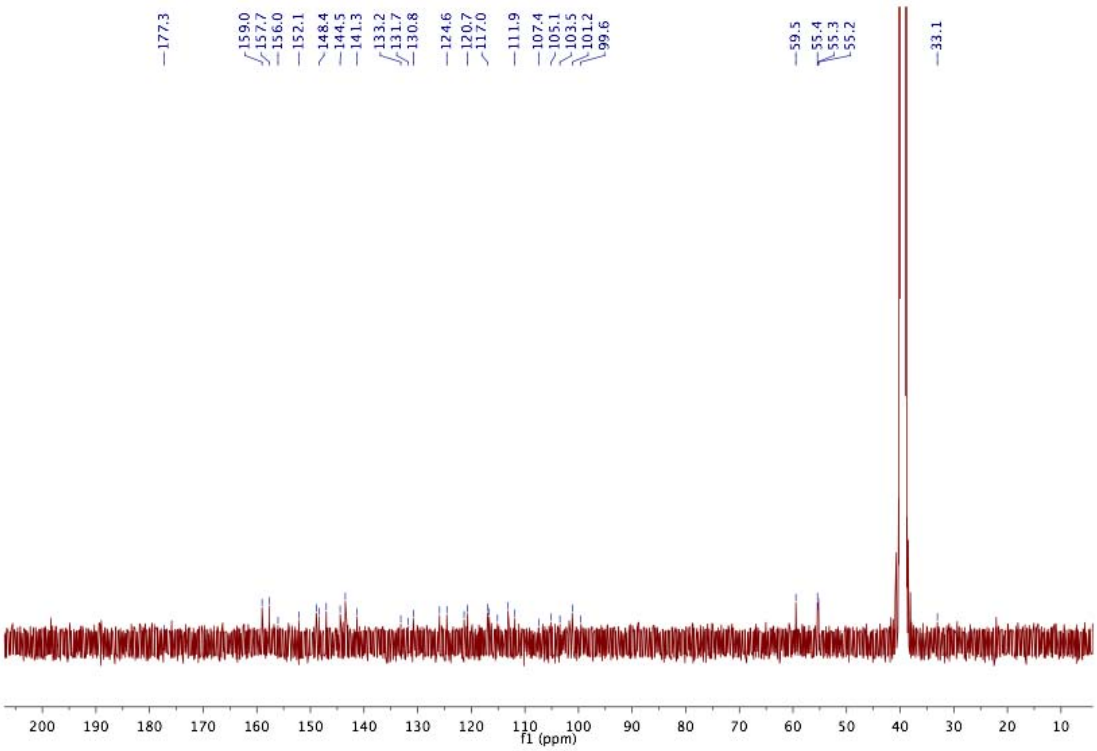

MeO
OMe
HO
OH

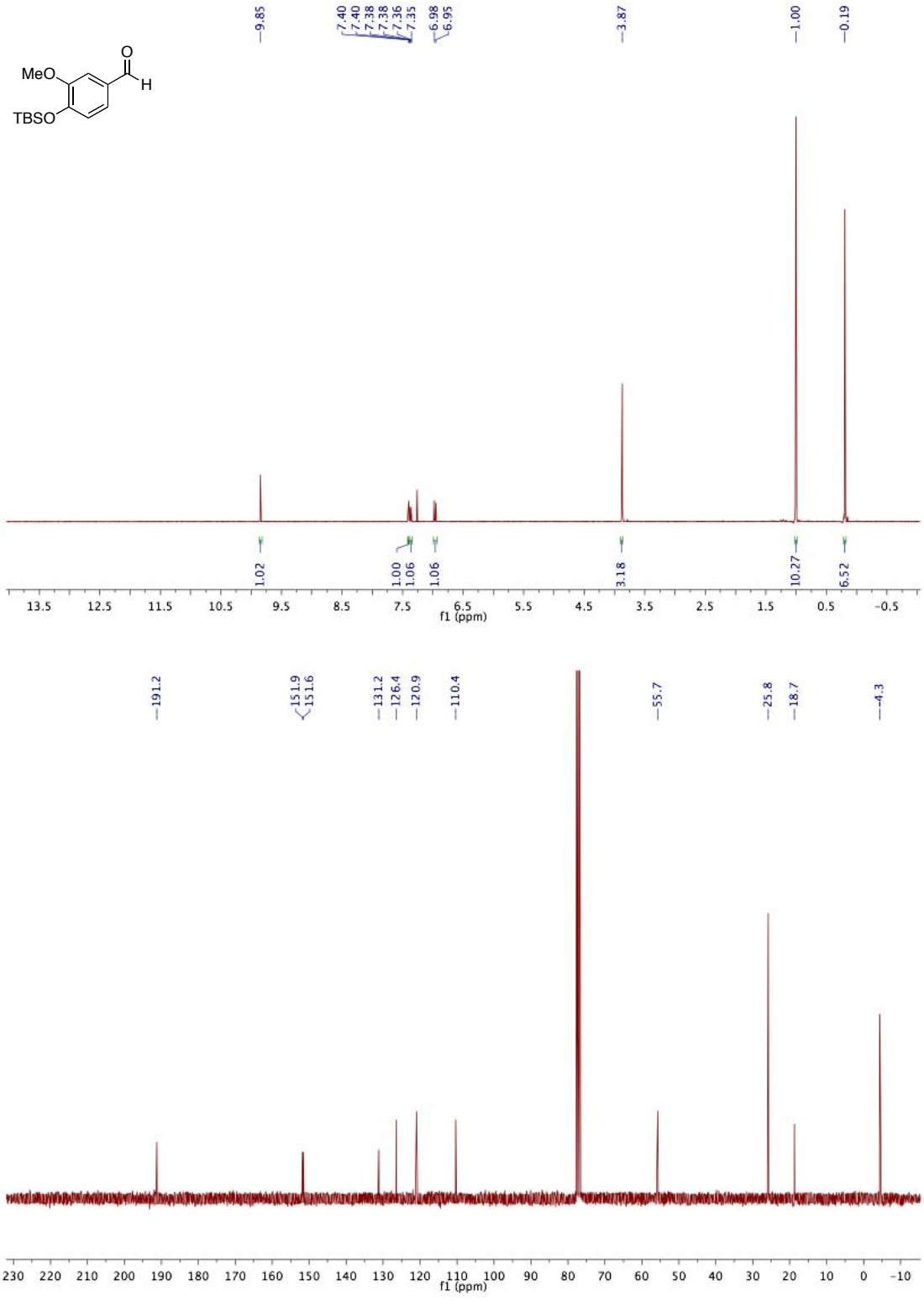
7.25
7.23
6.73
6.62
6.41
6.36
6.34
6.30
6.22
6.19
6.16
3.83
3.77
3.42
3.42
3.41
3.40
1.00
1.00
0.99
1.10
1.15
1.01
1.19
1.14
f1 (ppm)

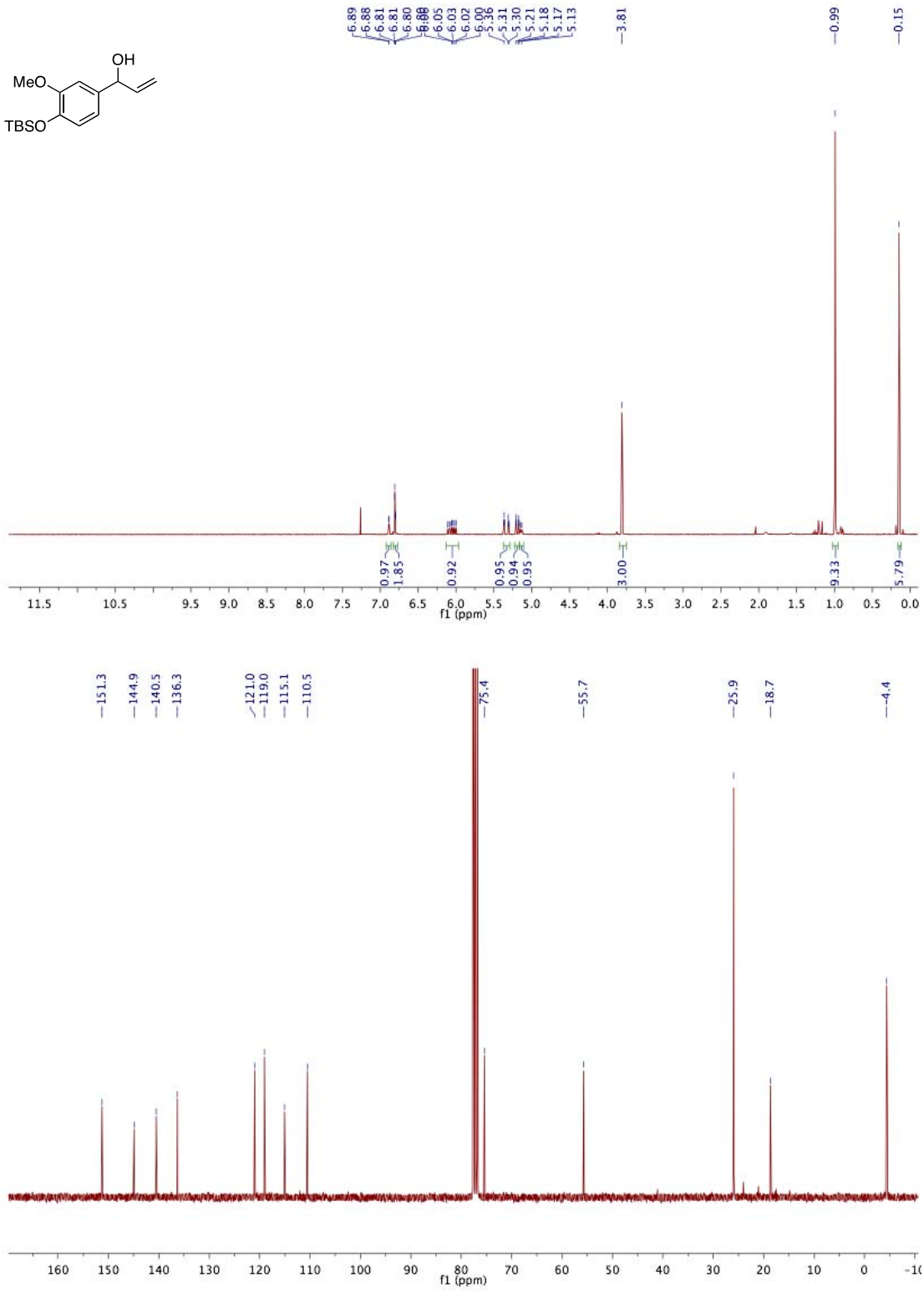

159.0
158.8
148.5
145.7
134.1
128.7
126.2
119.7
113.4
108.6
100.3
57.0
56.5
40.3
f1 (ppm)

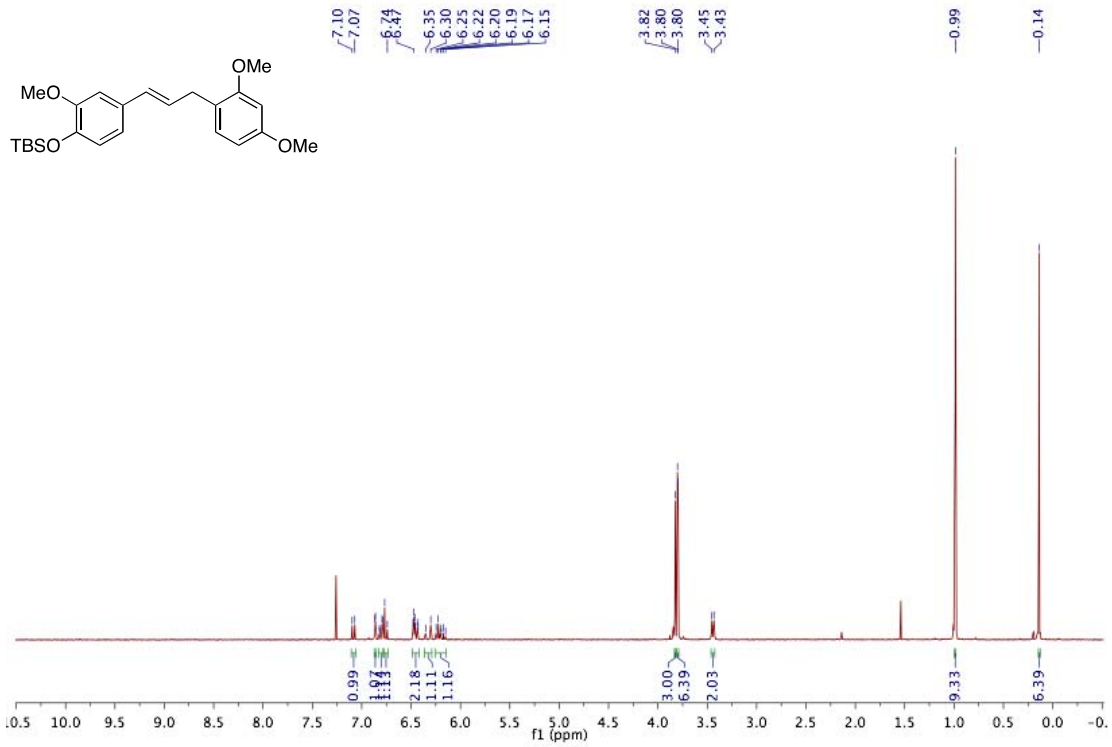


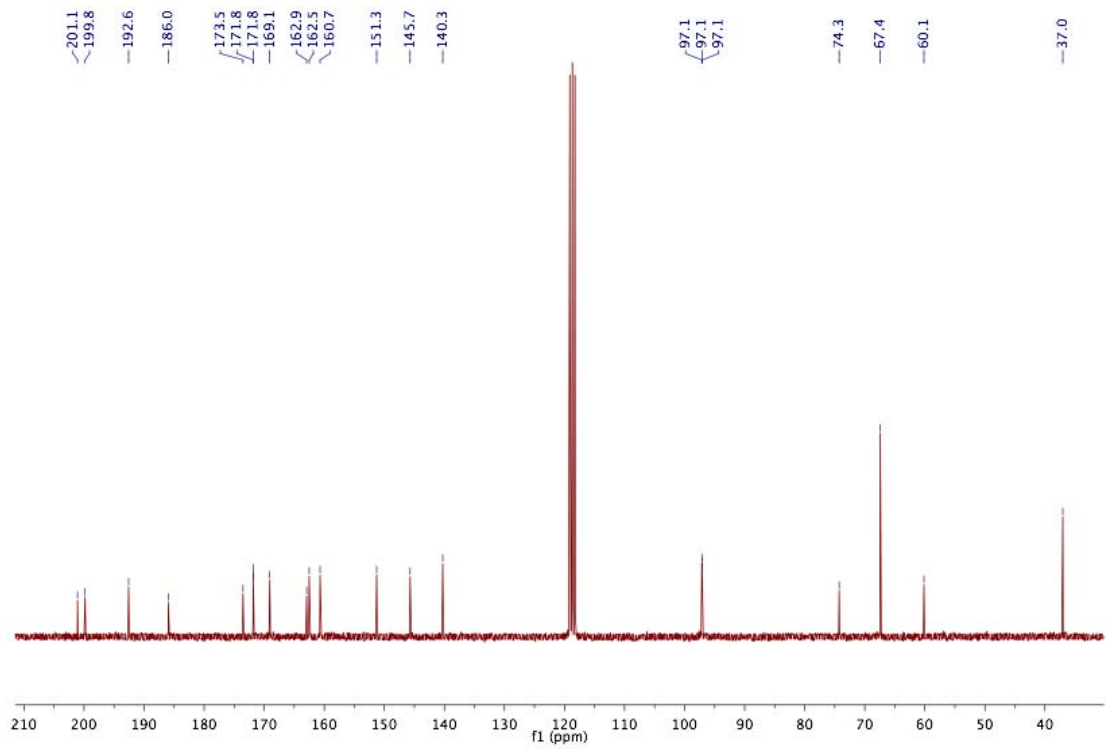
santalin B (**18**)

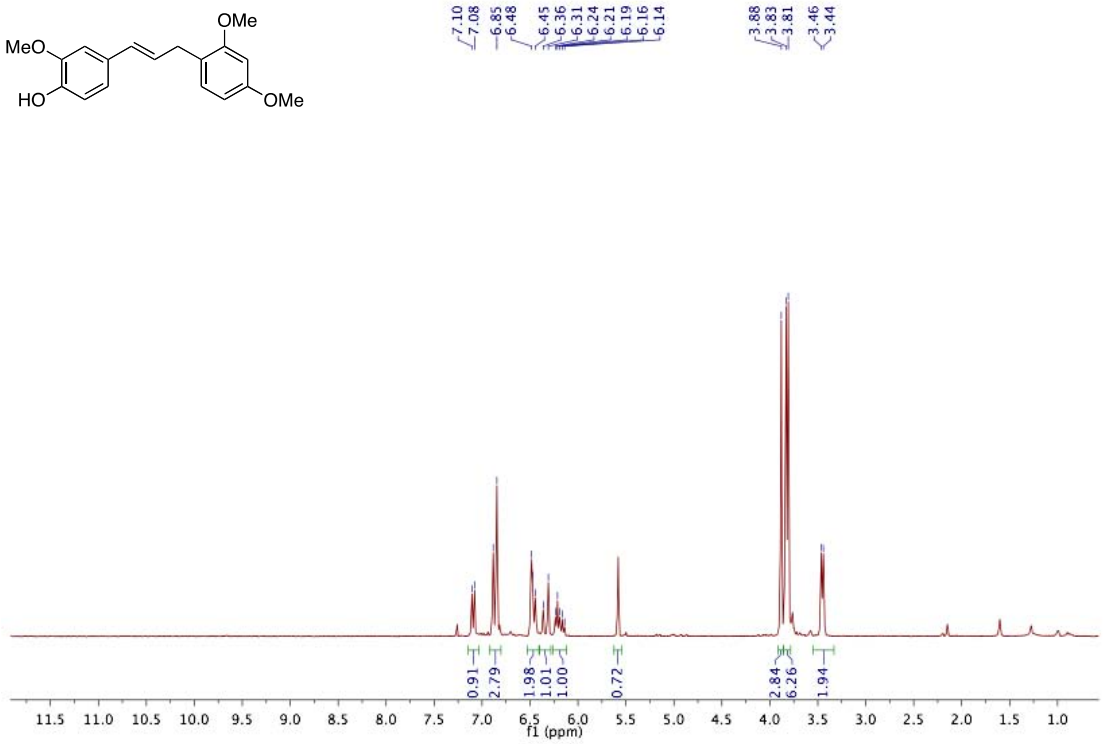


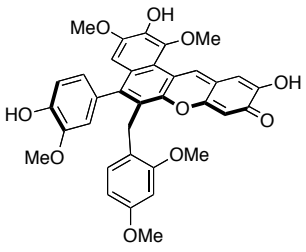

MeO
TBSO
O
H
9.85
7.40
7.40
7.38
7.38
7.36
7.35
6.98
6.95
3.87
1.00
0.19
1.02
1.00
1.06
1.06
3.18
10.27
6.52
f1 (ppm)
191.2
151.9
151.6
131.2
126.4
120.9
110.4
55.7
25.8
18.7
-4.3
f1 (ppm)


OH
MeO
TBSO
6.89
6.88
6.81
6.81
6.80
6.05
6.03
6.02
6.00
5.36
5.31
5.30
5.21
5.18
5.17
5.13
3.81
0.99
0.15
0.97
1.85
0.92
0.95
0.94
0.95
3.00
9.33
5.79
f1 (ppm)
151.3
144.9
140.5
136.3
121.0
119.0
115.1
110.5
75.4
55.7
25.9
18.7
-4.4
f1 (ppm)

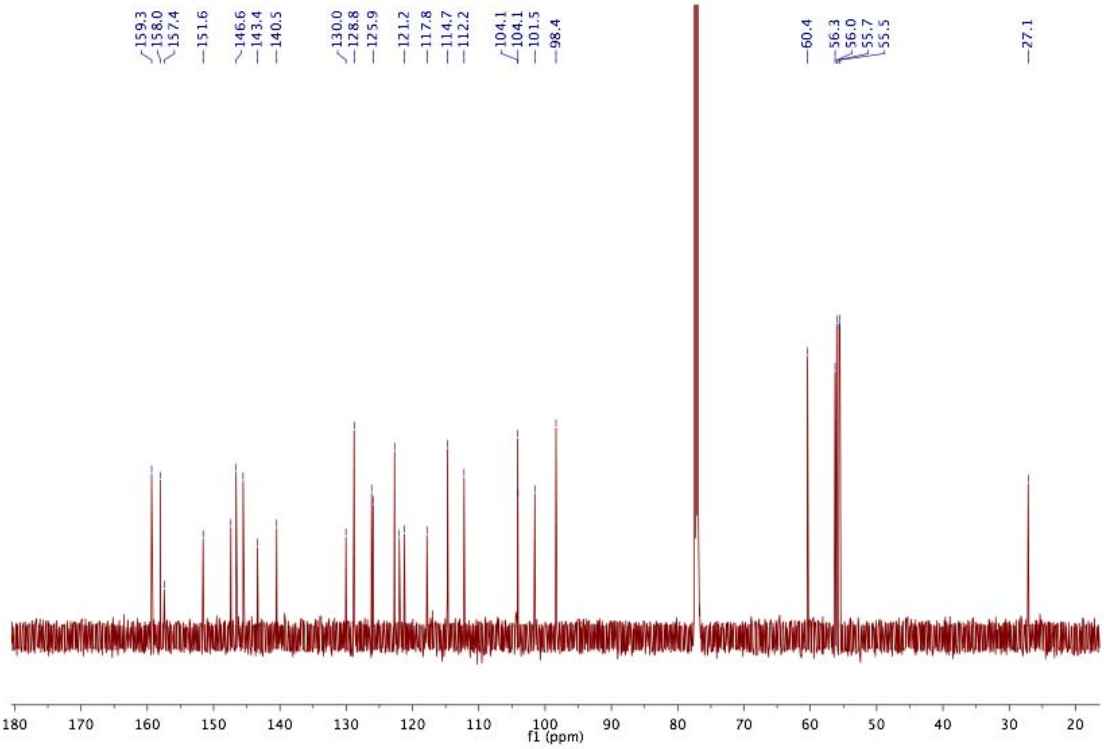

MeO
OMe
TBSO
OMe
f1 (ppm)

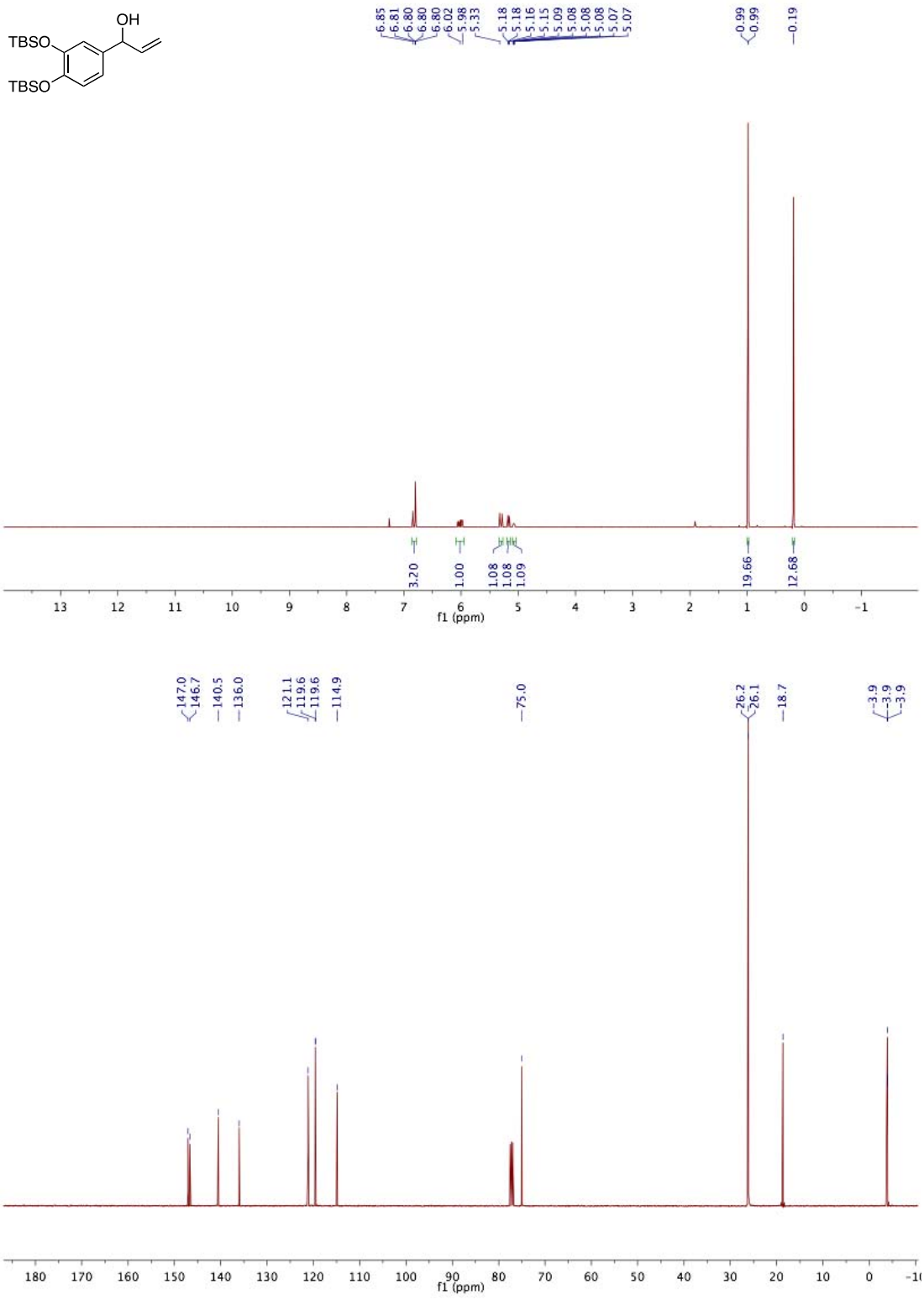

f1 (ppm)

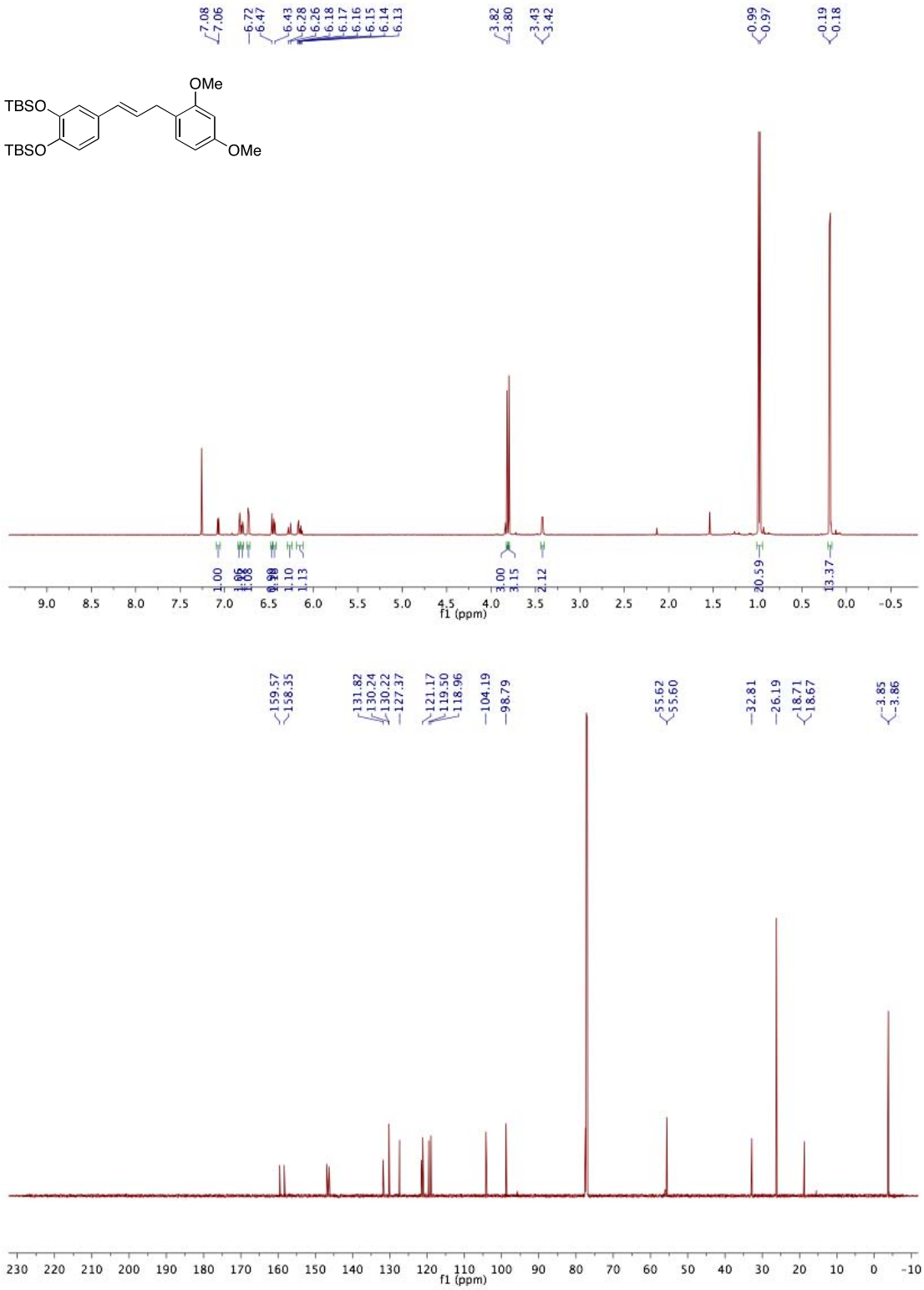

MeO
HO
OMe
OMe
7.10
7.08
6.85
6.48
6.45
6.36
6.31
6.24
6.21
6.19
6.16
6.14
3.88
3.83
3.81
3.46
3.44
0.91
2.79
1.98
1.01
1.00
0.72
2.84
6.26
1.94
f1 (ppm)
159.6
158.4
146.7
145.1
130.7
130.3
127.3
119.9
114.5
108.3
104.2
98.8
56.1
55.6
55.6
32.8
f1 (ppm)

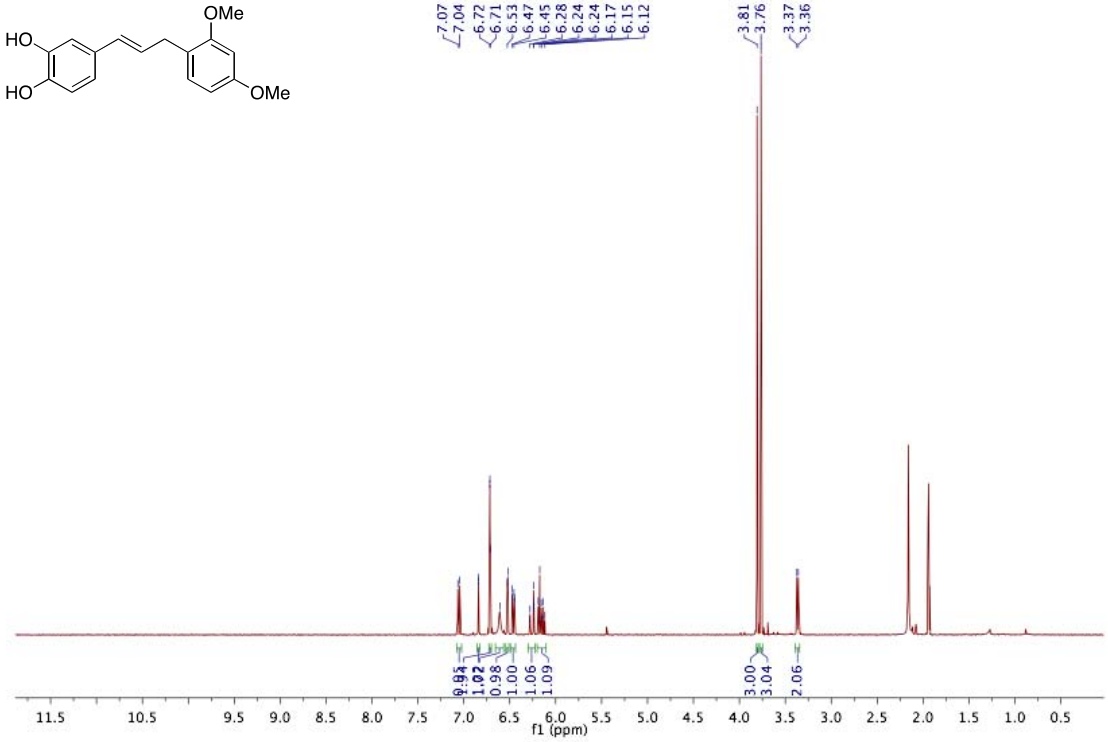


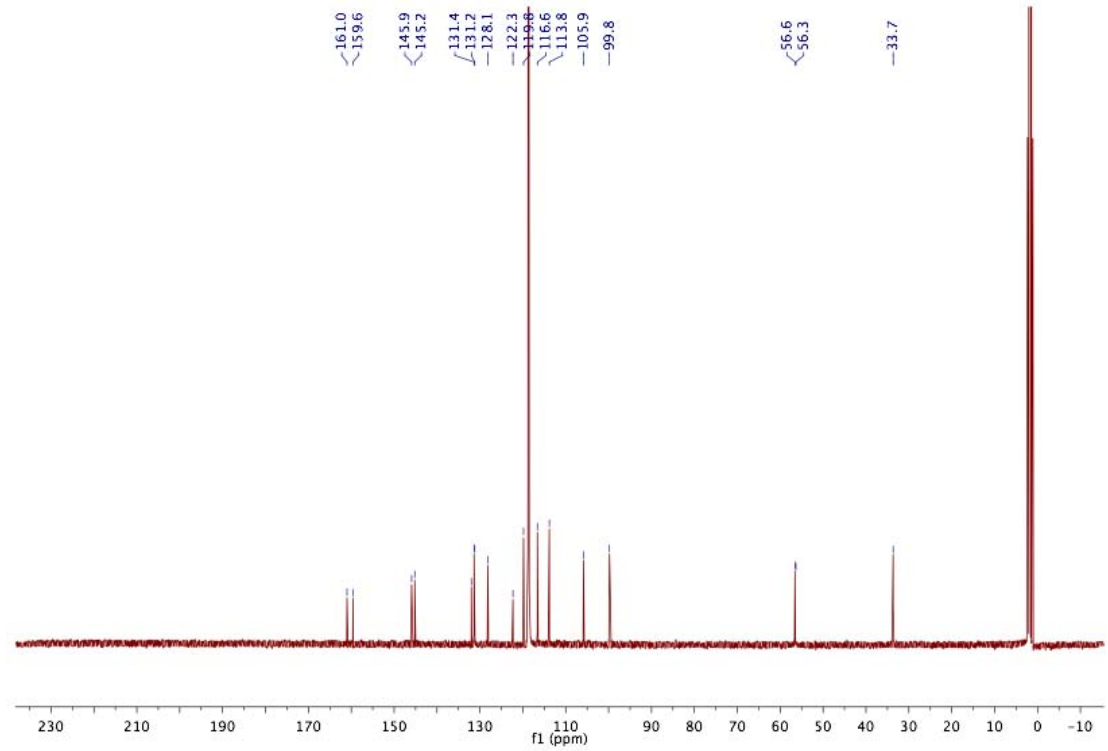
santarubin A (**19**)

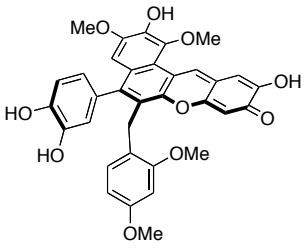



OH
TBSO
TBSO
6.85
6.81
6.80
6.80
6.80
6.02
5.98
5.33
5.18
5.18
5.16
5.15
5.09
5.08
5.08
5.08
5.07
5.07
0.99
0.99
0.19
3.20
1.00
1.08
1.08
1.09
19.66
12.68
f1 (ppm)
147.0
146.7
140.5
136.0
121.1
119.6
119.6
114.9
75.0
26.2
26.1
18.7
3.9
3.9
3.9
f1 (ppm)

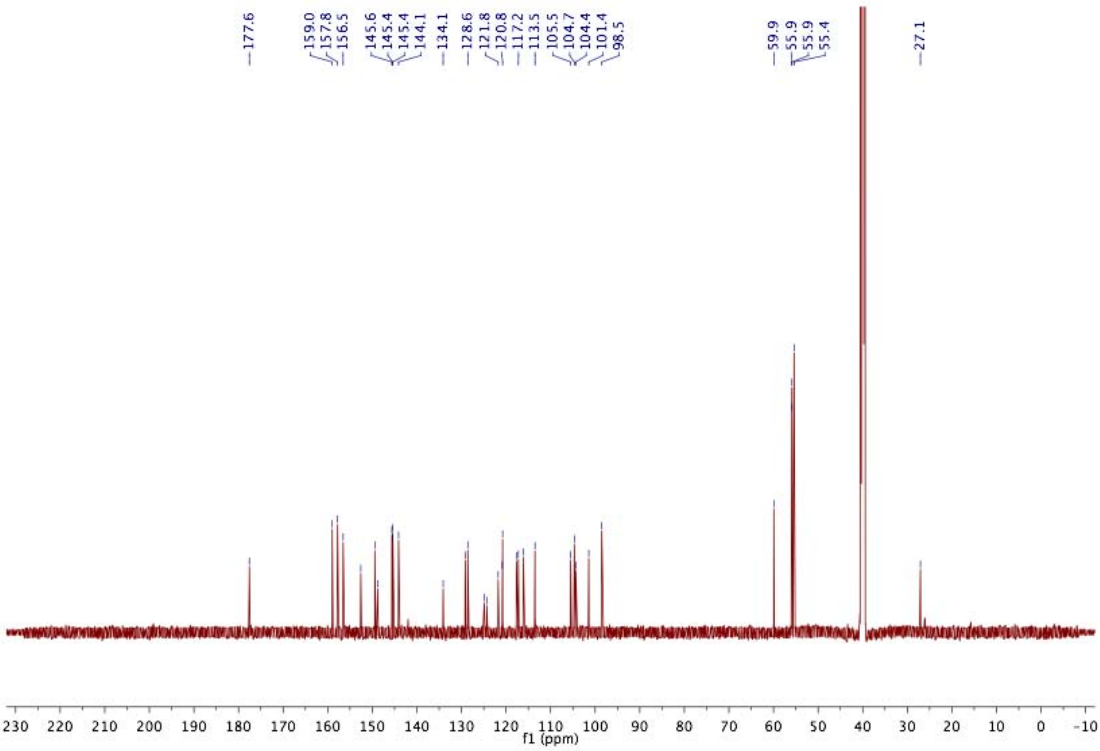

TBSO
TBSO
OMe
OMe
f1 (ppm)
f1 (ppm)


HO
HO
OMe
OMe
7.07
7.04
6.72
6.71
6.53
6.47
6.45
6.28
6.24
6.24
6.17
6.15
6.12
3.81
3.76
3.37
3.36
0.98
1.00
1.06
1.09
3.00
3.04
2.06
f1 (ppm)

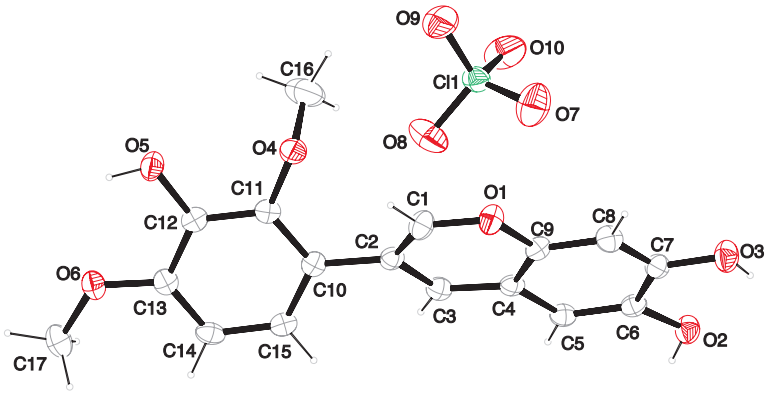

161.0
159.6
145.9
145.2
131.4
131.2
128.1
122.3
116.6
113.8
105.9
99.8
56.6
56.3
33.7
f1 (ppm)



santarubin B (**20**)

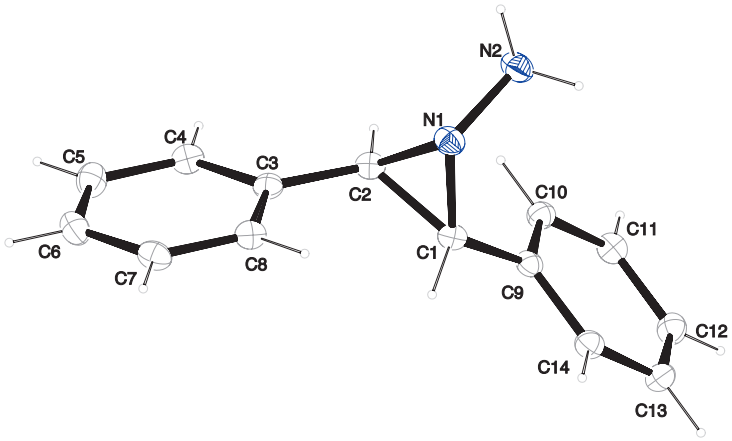


VIII. Appendix III – Crystal structures



	81
net formula	$C_{17}H_{15}ClO_{10}$
M_r/g mol^{-1}	414.748
crystal size/mm	0.30 × 0.21 × 0.16
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1/n$
a/Å	11.5176(11)
b/Å	12.5567(9)
c/Å	12.9588(13)
α/°	90
β/°	114.178(12)
γ/°	90
V/Å^3	1709.7(3)
Z	4
calc. density/g cm^{-3}	1.6113(3)
μ/mm^{-1}	0.283
absorption correction	'multi-scan'
transmission factor range	0.60526–1.00000
refls. measured	5834
R_{int}	0.0322
mean σ(I)/I	0.0510
θ range	4.20–26.37
observed refls.	2773
x, y (weighting scheme)	0.0568, 0.5985

hydrogen refinement	constr
refls in refinement	3463
parameters	258
restraints	0
$R(F_{obs})$	0.0451
$R_w(F^2)$	0.1251
S	1.045
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.271
min electron density/e Å^{-3}	−0.521



	111
net formula	$C_{14}H_{14}N_2$
M_r/g mol^{-1}	210.274
crystal size/mm	0.29 × 0.21 × 0.14
T/K	153(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	orthorhombic
space group	*Pbca*
a/Å	5.6864(6)
b/Å	18.4059(14)
c/Å	21.690(2)
α/°	90
β/°	90
γ/°	90
V/Å^3	2270.1(4)
Z	8

calc. density/g cm^{-3}	1.2305(2)
μ/mm^{-1}	0.074
absorption correction	'multi-scan'
transmission factor range	0.53991–1.00000
refls. measured	7194
R_{int}	0.0377
mean σ(I)/I	0.0367
θ range	4.20–26.36
observed refls.	1876
x, y (weighting scheme)	0.0484, 0.7336
hydrogen refinement	mixed
refls in refinement	2314
parameters	151
restraints	0
$R(F_{obs})$	0.0448
$R_w(F^2)$	0.1137
S	1.024
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.200
min electron density/e Å^{-3}	−0.198

IX. References

[1] A. Arnone, L. Camarda, L. Merlin, G. Nasini, *J. Chem. Soc., Perkin Trans. 1,* **1975**, 186–194.

[2] J. Kinjo, H. Uemura, T. Nohara, M. Yamashita, K. Yoshihira, *Tetrahedron Lett.* **1995**, *36*, 5599–5602.

[3] aM. C. de la Torre, M. A. Sierra, *Angew. Chem. Int. Ed.* **2004**, *43*, 160–181; bM. Razzak, J. K. De Brabander, *Nat. Chem. Biol.* **2011**, *7*, 865–875; cE. M. Stocking, R. M. Williams, *Angew. Chem. Int. Ed.* **2003**, *42*, 3078–3115.

[4] aS. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685–7688; bL. Klier, T. Bresser, T. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc.* **2012**, *134*, 13584–13587.

[5] H. Tsukamoto, T. Uchiyama, T. Suzuki, Y. Kondo, *Org. Biomol. Chem.* **2008**, *6*, 3005–3013.

[6] W. Rao, P. W. H. Chan, *Org. Biomol. Chem.* **2008**, *6*, 2426–2433.

[7] aA. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370; bA. K. Chatterjee, F. D. Toste, T.-L. Choi, R. H. Grubbs, *Adv. Synth. Catal.* **2002**, *344*, 634–637.

[8] P. M. Dewick, in *Medicinal natural products: A biosynthetic approach*, 3rd. ed., Wiley, **2009**, pp. 137–186.

[9] aE. Tripoli, M. L. Guardia, S. Giammanco, D. D. Majo, M. Giammanco, *Food Chem.* **2007**, *104*, 466–479; bJ.-Y. Pan, S.-L. Chen, M.-H. Yang, J. Wu, J. Sinkkonen, K. Zou, *Nat. Prod. Rep.* **2009**, *26*, 1251–1292; cS. Quideau, D. Deffieux, C. Douat-Casassus, L. Pouységu, *Angew. Chem. Int. Ed.* **2011**, *50*, 586–621.

[10] T. Shen, X.-N. Wang, H.-X. Lou, *Nat. Prod. Rep.* **2009**, *26*, 916–935.

[11] A. I. Scott, *Nature* **1960**, *186*, 556–556.

[12] N. A. Simonian, J. T. Coyle, *Annu. Rev. Pharmacol. Toxicol.* **1996**, *36*, 83–106.

[13] cited-in, *Ann. Phys. Chem.* **1833**, *29*, 102–107.

[14] aK. Gurudutt, T. Seshadri, *Phytochemistry* **1974**, *13*, 2845–2847; bA. Banerjee, A. Mukherjee, *Biotech. Histochem.* **1981**; cB. Ravindranath, T. R. Seshadri, *Tetrahedron Lett.* **1972**, *13*, 1201–1204.

[15] aA. Arnone, L. Camarda, L. Merlin, G. Nasini, *J. Chem. Soc., Perkin Trans. 1,* **1977**, 2118–2122; bA. Arnone, L. Camarda, L. Merlini, G. Nasini, D. A. H. Taylor, *J. Chem. Soc., Perkin Trans. 1,* **1977**, 2116–2118; cA. Arnone, L. Merlini, G. Nasini, *Tetrahedron Lett.* **1972**, *13*, 3503–3506.

[16] aA. Liepa, *Aust. J. Chem.* **1981**, *34*, 2647–2655; bA. J. Liepa, *Aust. J. Chem.* **1984**, *37*, 2545–2558.

[17] K. Brand, H. Collischonn, *J. Prakt. Chem.* **1921**, *103*, 2923–2925.

[18] M. Carmack, *J. Heterocycl. Chem.* **1989**, *26*, 1319–1323.

[19] M. S. C. Pedras, M. Suchy, *Bioorg. Med. Chem.* **2006**, *14*, 714–723.

[20] F. Hanawa, S. Tahara, J. Mizutani, *Phytochemistry* **1991**, *30*, 2197–2198.

[21] T. Kametani, K. Fukumoto, *J. Chem. Soc.* **1968**, 2156–2159.

[22] S. G. Levine, *J. Am. Chem. Soc.* **1958**, *80*, 6150–6151.

[23] W. Haefliger, D. Hauser, *Synthesis* **1980**, *3*, 236–238.

[24] L. M. Kabeya, A. A. de Marchi, A. Kanashiro, N. P. Lopes, C. H. T. P. da Silva, M. T. Pupo, Y. M. Lucisano-Valim, *Bioorg. Med. Chem.* **2007**, *15*, 1516–1524.

[25] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933.

[26] R. Giles, A. Hughes, M. Sargent, *J. Chem. Soc., Perkin Trans. 1,* **1991**, *6*, 1581–1587.

[27] A. Bagno, W. Kanthlehner, R. Kress, G. Saielli, *Z. Naturforsch.* **2004**, *59*, 386–397.

[28] Ø. W. Akselsen, L. Skattebøl, T. V. Hansen, *Tetrahedron Lett.* **2009**, *50*, 6339–6341.

[29] M.-S. Schiedel, C. A. Briehn, P. Bäuerle, *Angew. Chem. Int. Ed.* **2001**, *40*, 4677–4680.

[30] Y. A. Jackson, *Heterocycles* **1995**, *41*, 1979–1986.

[31] J. Potenziano, R. Spitale, M. E. Janik, *Synth. Comm.* **2005**, *35*, 2005–2016.

[32] R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461–1473.

[33] C. O. Kappe, *Angew. Chem. Int. Ed.* **2004**, *43*, 6250–6284.

[34] M. Mosrin, P. Knochel, *Org. Lett.* **2009**, *11*, 1837–1840.

[35] Q. Liu, Y. Lan, J. Liu, G. Li, Y.-D. Wu, A. Lei, *J. Am. Chem. Soc.* **2009**, *131*, 10201–10210.

[36] F. Ito, K. Fusegi, T. Kumamoto, T. Ishikawa, *Synthesis* **2007**, *12*, 1785–1796.

[37] L. C. Dias, L. G. de Oliveira, M. A. de Sousa, *Org. Lett.* **2003**, *5*, 265–268.

[38] aB. Gerard, G. Jones, J. A. Porco, *J. Am. Chem. Soc.* **2004**, *126*, 13620–13621; bJ. B. Hendrickson, J. S. Farina, *J. Org. Chem.* **1980**, *45*, 3359–3361.

[39] aB. Gerard, S. Sangji, D. J. O'Leary, J. A. Porco, *J. Am. Chem. Soc.* **2006**, *128*, 7754–7755; bB. Gerard, R. Cencic, J. Pelletier, J. A. Porco, *Angew. Chem. Int. Ed.* **2007**, *46*, 7831–7834; cN. J. Lajkiewicz, S. P. Roche, B. Gerard, J. A. Porco, *J. Am. Chem. Soc.* **2012**, *134*, 13108–13113; dP. A. Roethle, P. T. Hernandez, D. Trauner, *Org. Lett.* **2006**, *8*, 5901–5904; eP. A. Wender, H. Y. Lee, R. S. Wilhelm, P. D. Williams, *J. Am. Chem. Soc.* **1989**, *111*, 8954–8957.

[40] A. Padwa, *Acc. Chem. Res.* **1991**, *24*, 22–28.

[41] aR. K. Müller, R. Joos, D. Felix, J. Schreiber, C. Wintner, A. Eschenmoser, *Org. Synth.* **1976**, *55*, 114; bA. Padwa, D. J. Austin, Y. Gareau, J. M. Kassir, S. L. Xu, *J. Am. Chem. Soc.* **1993**, *115*, 2637–2647.

[42] H. Sasai, T. Suzuki, S. Arai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1992**, *114*, 4418-4420.

[43] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

[44] M. Kimura, M. Fukasaka, Y. Tamaru, *Synthesis* **2006**, *21*, 3611–3616.

[45] A. K. Chakraborti, L. Sharma, M. K. Nayak, *J. Org. Chem.* **2002**, *67*, 2541–2547.

[46] M. Mayer, W. M. Czaplik, A. Jacobi von Wangelin, *Adv. Synth. Catal.* **2010**, *352*, 2147–2152.

[47] H. Zheng, M. Lejkowski, D. G. Hall, *Chem. Sci.* **2011**, *2*, 1305–1310.

[48] I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066.

[49] M. Kamiya, H. Kobayashi, Y. Hama, Y. Koyama, M. Bernardo, T. Nagano, P. L. Choyke, Y. Urano, *J. Am. Chem. Soc.* **2007**, *129*, 3918–3929.

[50] A. Ozanne, L. Pouységu, D. Depernet, B. François, S. Quideau, *Org. Lett.* **2003**, *5*, 2903–2906.

[51] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

[52] D. M. X. Donnelly, P. J. Keenan, J. P. Prendergast, *Phytochemistry* **1973**, *12*, 1157–1161.

[53] T. Kametani, K. Fukumoto, *J. Chem. Soc. C* **1968**, *0*, 2156–2159.

[54] M. Femenía-Ríos, C. M. García-Pajón, R. Hernández-Galán, A. J. Macías-Sánchez, I. G. Collado, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5836–5839.

[55] F. C. Gozzo, S. A. Fernandes, D. C. Rodrigues, M. N. Eberlin, A. J. Marsaioli, *J. Org. Chem.* **2003**, *68*, 5493–5499.

[56] B. D. Gates, P. Dalidowicz, A. Tebben, S. Wang, J. S. Swenton, *J. Org. Chem.* **1992**, *57*, 2135–2143.

[57] V. M. Swamy, P. Ilankumaran, S. Chandrasekaran, *Synlett* **1997**, *SI*, 513–514.

[58] C. A. Faler, M. M. Joullié, *Org. Lett.* **2007**, *9*, 1987–1990.

[59] R. Tello-Aburto, A. M. Harned, *Org. Lett.* **2009**, *11*, 3998–4000.

[60] S. Matsumoto, T. Asakawa, Y. Hamashima, T. Kan, *Synlett* **2012**, *7*, 1082–1084.

[61] A. A. Camacho-Dávila, *Synth. Commun.* **2008**, *38*, 3823–3833.

[62] A. Yahya-Meymandi, G. Mohammadi Ziarani, A. Shafiee, A. Foroumadi, *Asian J. Chem.* **2011**, 4008–4010.

[63] A. Ramacciotti, R. Fiaschi, E. Napolitano, *Tetrahedron: Asymmetry* **1996**, *7*, 1101–1104.

[64] Y. Yamamoto, N. Kirai, *Org. Lett.* **2008**, *10*, 5513–5516.

[65] S. Quideau, M. Lebon, A.-M. Lamidey, *Org. Lett.* **2002**, *4*, 3975–3978.

[66] T. Sawada, M. Nakada, *Adv. Synth. Catal.* **2005**, *347*, 1527–1532.

[67] V. Bhalla, H. Singh, M. Kumar, *Org. Lett.* **2009**, *12*, 628–631.

[68] M. E. Bos, W. D. Wulff, R. A. Miller, S. Chamberlin, T. A. Brandvold, *J. Am. Chem. Soc.* **1991**, *113*, 9293–9319.

[69] M. A. Khalilzadeh, A. Hosseini, M. Shokrollahzadeh, M. R. Halvagar, D. Ahmadi, F. Mohannazadeh, M. Tajbakhsh, *Tetrahedron Lett.* **2006**, *47*, 3525–3528.

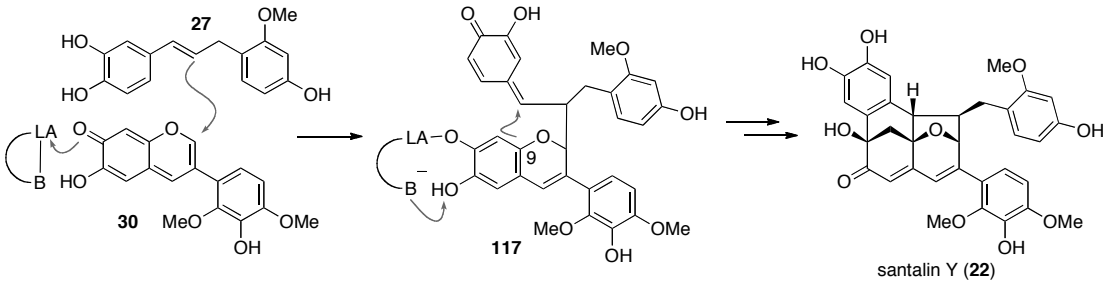
[70] F. Fache, N. Suzan, O. Piva, *Tetrahedron* **2005**, *61*, 5261–5266.

[71] A. K. Chakraborti, L. Sharma, M. K. Nayak, *J. Org. Chem.* **2002**, *67*, 2541–2547.

[72] J. Chen, X. Chen, M. Willot, J. Zhu, *Angew. Chem. Int. Ed.* **2006**, *45*, 8028–8032.

Addendum

A possible solution in the biomimetic synthesis of santalin Y (22) has been mentioned previously in the final chapter IV "Summary, Conclusion and Future Directions" of this thesis. It has been proposed that a generic bifunctional catalyst, shown in **Scheme 103**, can coordinate to the carbonyl function with simultanious activation of a Brønstedt basic site (B). The Brønstedt base enhances deprotonation of the vicinal hydroxy-group, thus favoring the attack to the *ortho*-quinone methide leading to santalin Y (**22**).



Scheme 103 – Hypothesis for the biomimetic formation of santalin Y.

Due to the presence of catechol units with metal chelating properties, organocatalytic bifunctional catalysts were preferred to bimetallic catalysts developed by the group of Shibasaki[42]. A thiourea-based catalyst **119**, developed by the group of Takemoto[43], with a tertiary amine in close proximity, was chosen (**Figure 17**).

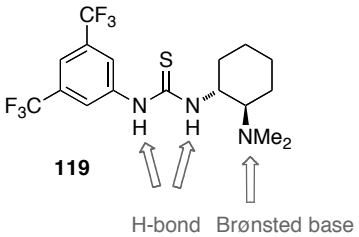
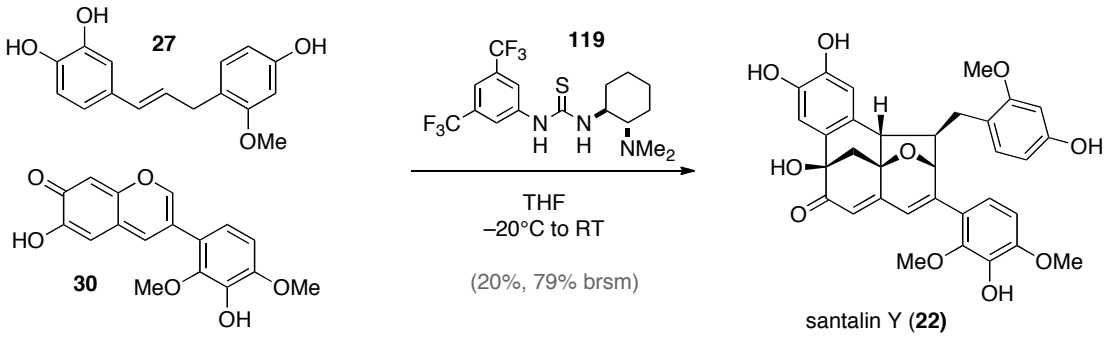


Figure 17 – Takemoto's bifunctional catalyst.

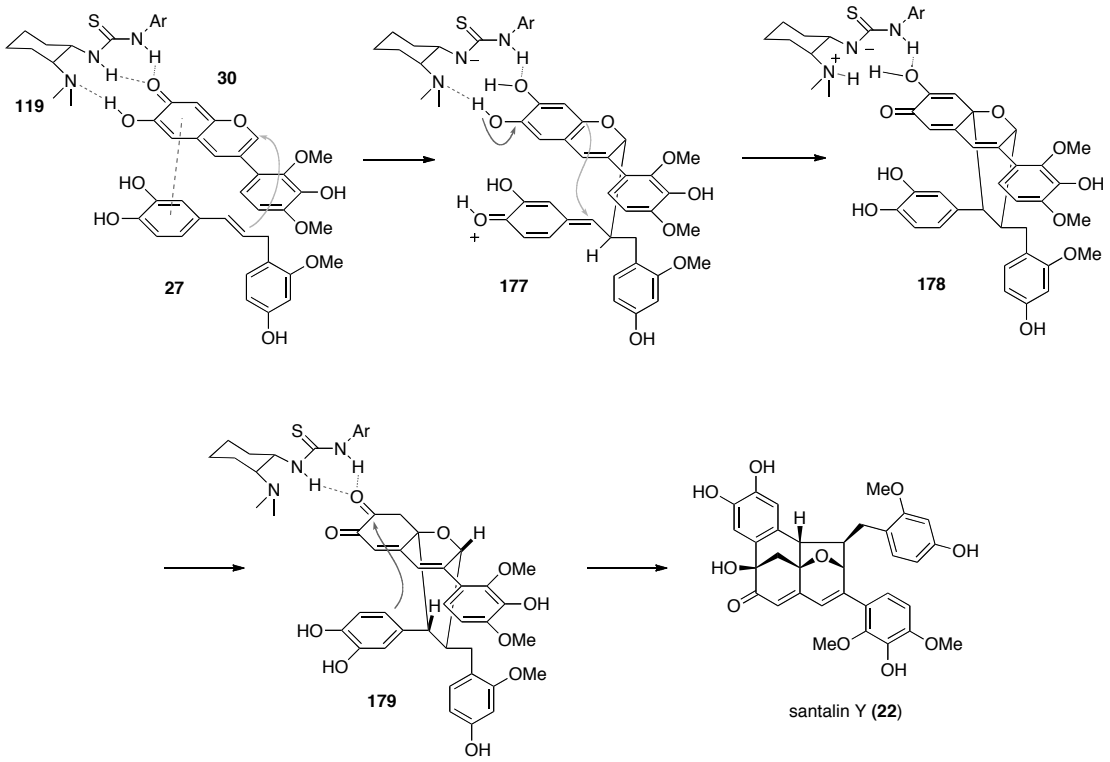
Formation of santalin Y can be observed in moderate yield with unreacted starting material still present (**Scheme 104**). An increase of the catalyst loading to

stochiometric amounts or a different Brønstedt-basic subunit, making the amine more basic, might favor full conversion.



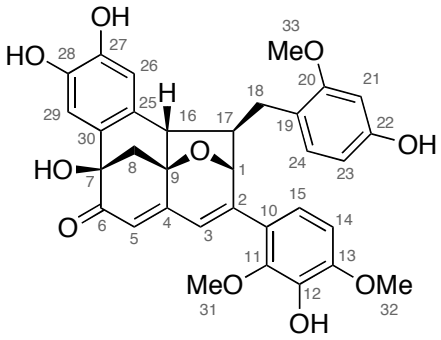
Scheme 104 – Biosynthetic assembly of santalin Y (**22**).

Our proposed mechanism describes a vinylogous attack of the benzylstyrene **27** to the anhydrobase **30**, which coordinates the catalyst **119** by hydrogen-bonds. Due to the Brønstedt-basic site in close proximity to the thiourea unit, deprotonation can only take place at the vicinal hydroxy group thus favoring the attack of the chromane heterocycle leading to cyclohepten **178**. Subsequent keto-enol tautomerization and activation of the resulting carbonylfunction by the thiourea catalyst facilitates a Friedel-Crafts type attack to result in santalin Y (22) (**Scheme 105**).



Scheme 105 – Proposed mechanism using Takemoto's catalyst (**119**).

Santalin Y (22)



To a stirred solution of anhydrobase **30** (10 mg, 0.031 mmol, 1 eq.) and benzylstyrene **27** (8.7 mg, 0.031 mmol, 1 eq.) in THF (1.3 mL) was added racemic thiourea catalyst **119** (2.6 mg, 0.006 mmol, 20 mol-%) at –20°C. The reaction mixture was allowed to come to room temperature and was stirred for 2 d. After the set time, the reaction mixture was concentrated *in vacuo*. Sequential purification with a

sephadex column (LH-20, MeOH) and preparative TLC (CH_2Cl_2:MeOH 10:1) afforded santalin Y (**20**) (4 mg, 22%) and benzylstyrene **27** (6.5 mg).

R_f = 0.38 (CH_2Cl_2:MeOH 9:1).

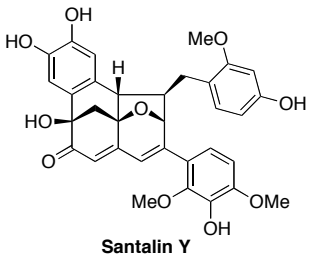
UV (MeCN): λ_{max} = 357 nm.

IR (ATR): $\tilde{\nu}$ = 3271 (m), 2925 (s), 2854 (s), 1733 (w), 1666 (m), 1596 (m), 1508 (m), 1462 (m), 1381 (w), 1278 (s), 1243 (m), 1176 (s), 1131 (s), 1024 (s), 1005 (m) cm^{-1}.

HRMS (ESI): calcd. for $C_{33}H_{31}O_{10}^+$ $[M+H]^+$: 587.1912,
found: 587.1918.

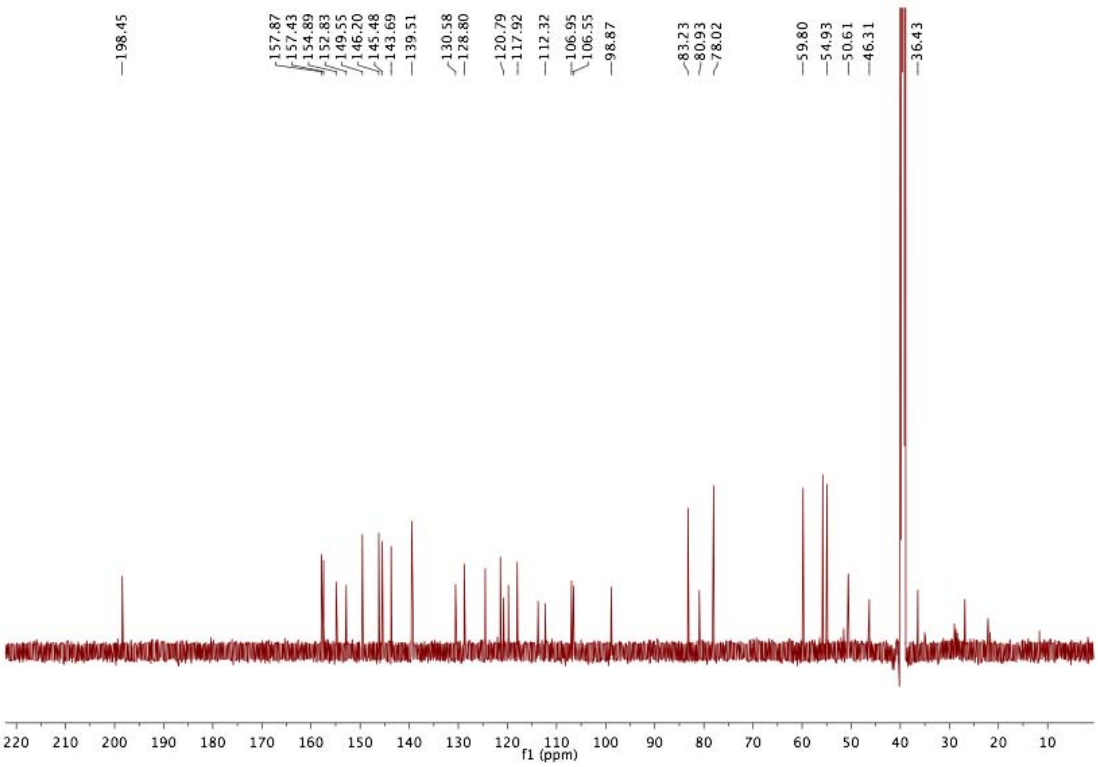
Number	^{1}H (d_6-DMSO, 600 MHz) Synthetic	^{13}C (d_6-DMSO, 150 MHz) Synthetic	^{1}H (d_6-DMSO, 600 MHz) Isolated	^{13}C (d_6-DMSO, 150 MHz) Isolated
OH	9.21 (s, 1H)			
OH	8.88 (s, 1H)			
OH	8.78 (s, 1H)			
OH	8.66 (s, 1H)			
OH	5.82 (s, 1H)			
1	4.84 (s, 1H)	80.93	4.85 (s, 1H)	80.9
2		152.83		152.9
3	6.36 (s, 1H)	120.79	6.36 (s, 1H)	120.8
4		154.89		154.9
5	5.62 (d, J = 0.6 Hz, 1H)	119.73	5.62 (s, 1H)	119.8
6		198.45		198.4
7		78.02		78.0
8	2.47, 2.62 (ABq, J = 10.7 Hz, 2H)	46.31	2.48, 2.62 (ABq, J = 10.6 Hz, 2H)	46.3
9		83.23		83.2
10		121.51		121.5
11		146.20		146.2
12		139.51		139.5
13		149.55		149.6
14	6.42 (d, J = 8.9 Hz,	106.95	6.43 (d, J = 8.8 Hz,	107.0

	1H)		1H)	
15	6.07 (d, *J* = 8.8 Hz)	117.92	6.08 (d, *J* = 8.8 Hz, 1H)	117.9
16	3.30 (m, 1H)	54.96	3.32 (m, 1H)	54.9
17	2.46 (m, 1H)	50.61	2.46 (m, 1H)	50.6
18	2.67 (dd, *J* = 13.8, 10.3 Hz, 1H), 3.00 (dd, *J* = 13.8, 4.0 Hz, 1H)	36.43	2.68 (dd, *J* = 13.7, 10.2 Hz, 1H), 3.00 (dd, *J* = 13.7, 3.6 Hz, 1H)	36.4
19		118.06		118.0
20		157.87		157.9
21	6.27 (d, *J* = 2.3 Hz, 1H)	98.87	6.27 (d, *J* = 2.2 Hz, 1H)	98.9
22		157.43		157.4
23	6.18 (dd, *J* = 8.0, 2.3 Hz, 1H)	106.55	6.19 (dd, *J* = 8.1, 2.2 Hz, 1H)	106.6
24	6.91 (d, *J* = 8.1 Hz, 1H)	130.58	6.91 (d, *J* = 8.1 Hz, 1H)	130.6
25		124.56		124.5
26	6.81 (s, 1H)	113.78	6.81 (s, 1H)	113.8
27		145.48		145.5
28		143.69		143.7
29	6.50 (d, *J* = 0.8 Hz, 1H)	112.32	6.51 (s, 1H)	112.3
30		128.80		128.8
31	3.56 (s, 3H)	59.80	3.55 (s, 3H)	59.8
32	3.77 (s, 3H)	55.79	3.77 (s, 3H)	55.8
33	3.66 (s, 3H)	54.93	3.67 (s, 3H)	55.0


OH
HO
MeO
H
OH
HO
O
O
MeO
OMe
OH

Santalin Y

9.21
8.88
8.78
8.66
6.92
6.91
6.81
6.36
6.19
6.07
5.82
5.62
5.62
4.84
3.77
3.66
3.56
3.30
2.99
2.69
2.68
2.67
2.65
2.63
2.62
2.62
2.61
2.61
2.48
2.46
0.97
1.02
0.94
0.99
0.97
1.09
1.03
0.93
1.02
3.09
3.04
2.98
1.00
1.03
2.27
1.95
f1 (ppm)


198.45
157.87
157.43
154.89
152.83
149.55
146.20
145.48
143.69
139.51
130.58
128.80
120.79
117.92
112.32
106.95
106.55
98.87
83.23
80.93
78.02
59.80
54.93
50.61
46.31
36.43
f1 (ppm)